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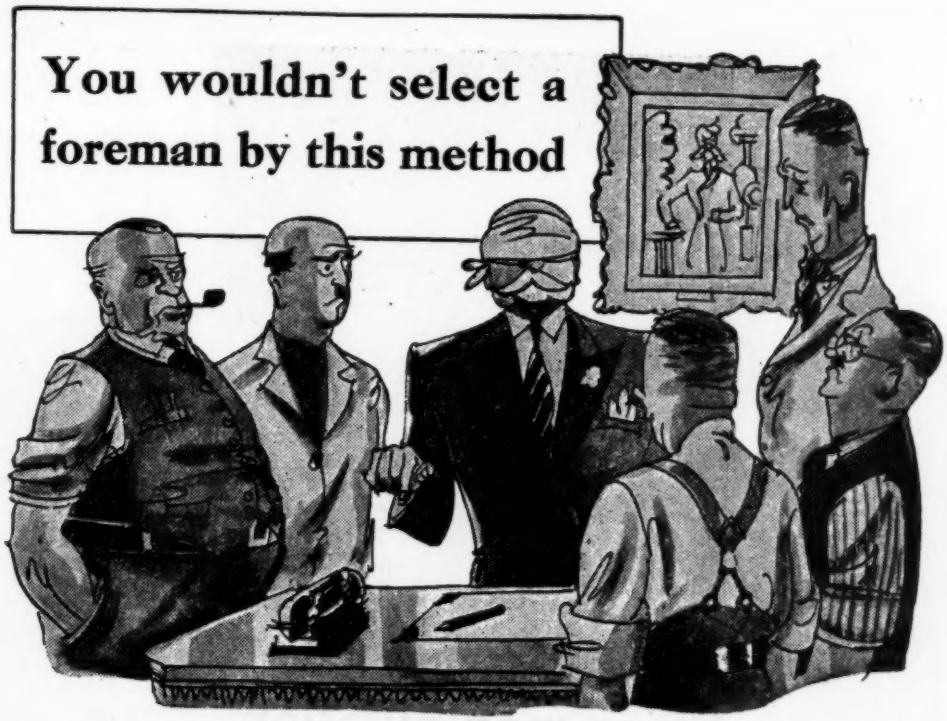

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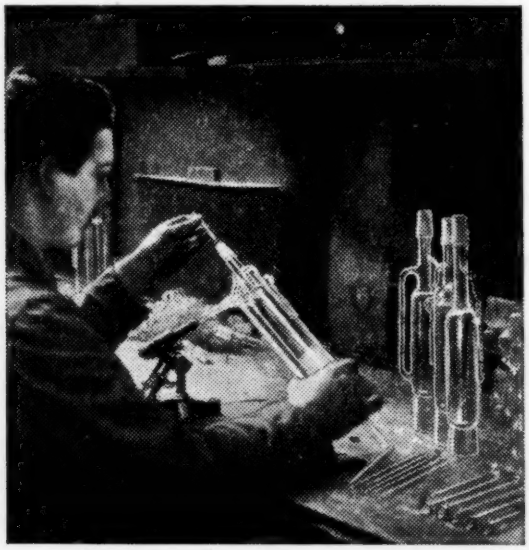

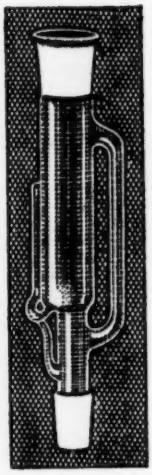

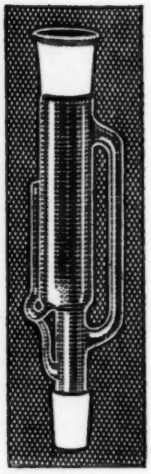

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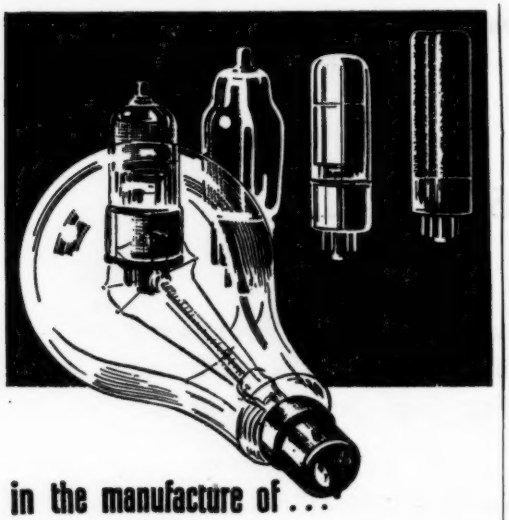

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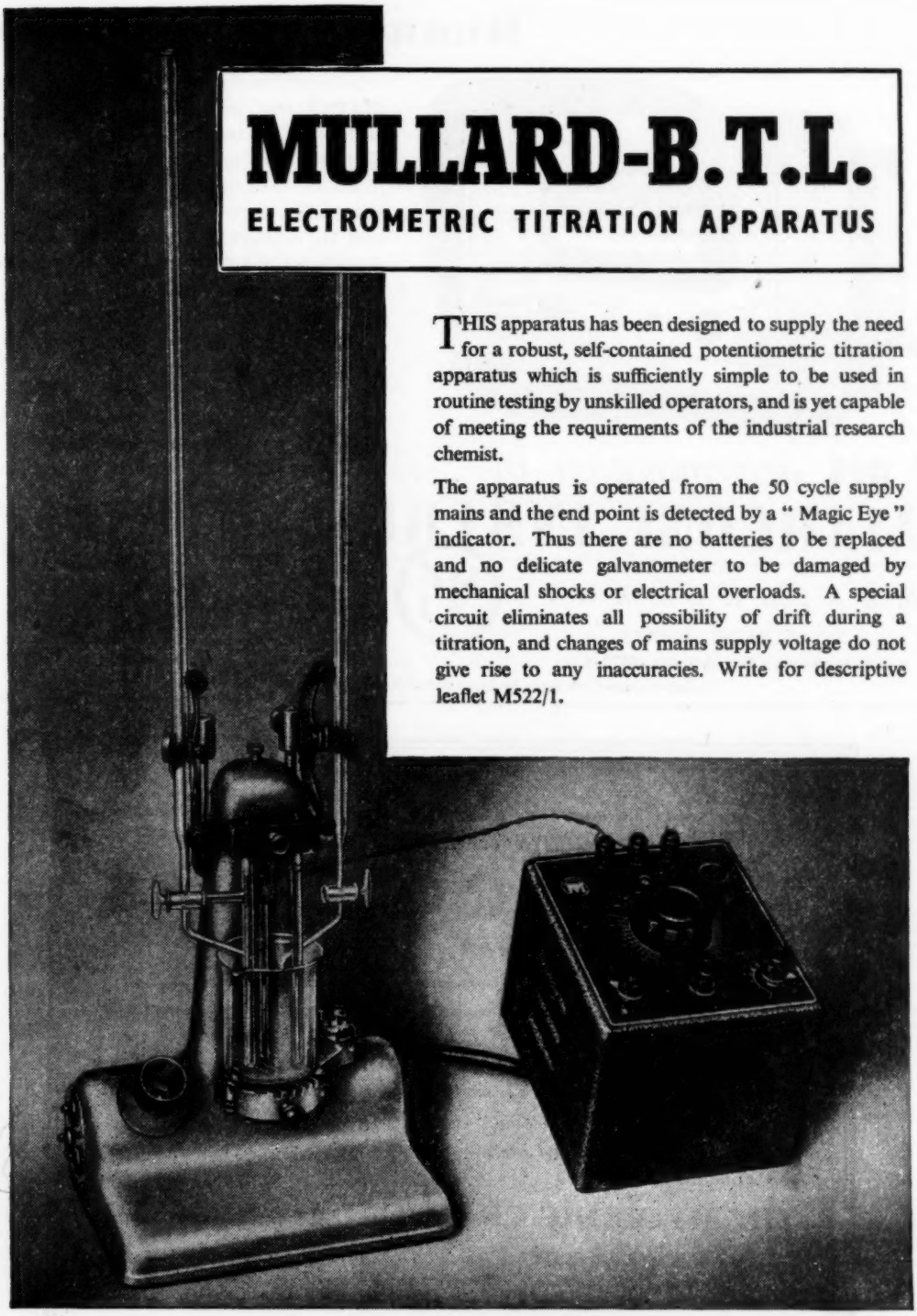

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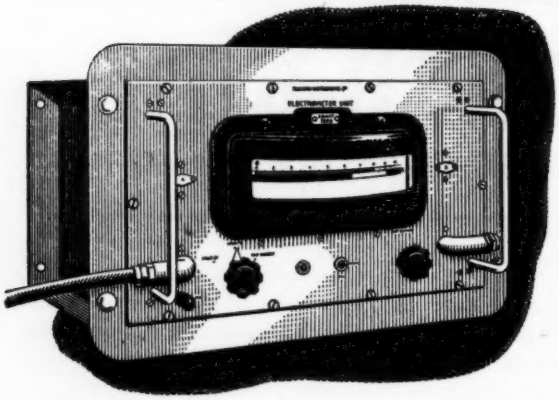

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CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

188. Nitration in Sulphuric Acid. Part I. The Nature of the Nitrating Agent in Nitric–Sulphuric Acid Mixtures.
By G. M. Bennett, J. C. D. Brand, and Gwyn Williams 869

189. Nitration in Sulphuric Acid. Part II. Migration of Nitric Acid to the Cathode during Electrolysis in Oleum Solution.
By G. M. Bennett, J. C. D. Brand, and Gwyn Williams 875

190. Nitration in Sulphuric Acid. Part III. The Influence of Nitric Acid and Other Substances upon the Oleum–Water Titration.
By John C. D. Brand 880

196. The Vapour Pressure of Phthalic Anhydride.
By D. A. Crooks and (Miss) F. M. Feetham. 899

197 The Estimation of Sulphur Trioxide in its Mixtures with Sulphur Dioxide by the Method of Amperometric Titration.
By D. W. E. Axford and T. M. Sugden 901

202. The Kinetics of Absorption of Gases from an Air Stream by Granular Reagents.
By C. J. Danby, J. G. Davoud, D. H. Everett, C. N. Hinshelwood, and R. M. Lodge . . 918

Organic.

183. Experiments on the Synthesis of Purine Nucleosides. Part XIII. An Improved Method for the Cyclisation of 4-Glycosidamino-5-thioformamidopyrimidines.
By G. W. Kenner and A. R. Todd 852

184. Experiments on the Synthesis of Purine Nucleosides. Part XIV. An Interpretation of Some Interconversion Reactions of *N*-Glycosides.
By G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd 855

185. Experiments on the Synthesis of Purine Nucleosides. Part XV. The Configuration of Some Synthetic Purine and Pyrimidine Glycosides.
By G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd 861

186. Some *p*-Alkoxybenzenesulphonamides and their *N*-Chloro-derivatives.
By W. E. Hanby and H. N. Rydon 865

187. Studies in the Polyene Series. Part XXIV. The C_{17} Acid and C_{18} Ketone related to Vitamin A.
By Sir Ian Heilbron, E. R. H. Jones, and D. G. O'Sullivan 866

191. New Syntheses of Heterocyclic Compounds. Part VII. 9-Amino-6 : 8-dimethyl-7 : 10-diazaphenanthrenes.
Vladimir A. Petrow 884

192. New Syntheses of Heterocyclic Compounds. Part VIII. The Schmidt Rearrangement of 1 : 3-Dimethyl-2-azafluorenones (continued).
By Vladimir A. Petrow 888

193. Strychnine. Part II.
By G. R. Clemo and R. Raper 891

194. Experiments on the Synthesis of the Pyrethrins. Part II. The Structure of Cinerone.
By Stanley H. Harper 892

195. Synthesis of 2-Arylfurans.
By A. W. Johnson 895

198. Strychnine and Brucine. Part XLII. Constitution of the *neo*-Series of Bases and their Oxidation Products.
By L. H. Briggs, H. T. Openshaw, and Sir Robert Robinson 903

199. Strychnine and Brucine. Part XLIII. Cuninecarboxylic Acid.
By H. L. Holmes, H. T. Openshaw, and Sir Robert Robinson 908

200. Strychnine and Brucine. Part XLIV. Synthetical Experiments. Part II.
By H. L. Holmes, H. T. Openshaw, and Sir Robert Robinson 910

201. Strychnine and Brucine. Part XLV. Synthetical Experiments. Part III.
By H. T. Openshaw and Sir Robert Robinson 912

203. 4-*n*-Propyl-picolinic and -pipecolinic Acids. Limitations of the Wibaut–Arens Reaction with α-Substituted Pyridine Derivatives.
By W. Solomon 934

PAGE

204. Researches on Acetylenic Compounds. Part VI. Carbinols derived from Methyl β-Chlorovinyl Ketone and their Conversion into Unsaturated Aldehydes.
By E. R. H. JONES and B. C. L. WEEDON 937

205. Researches on Acetylenic Compounds. Part VII. Reactions of 2-Chlorohex-3-en-5-yne and Related Compounds with Ammonia and Amines. Reversed Anionotropic Rearrangements accompanying Replacement.
By E. R. H. JONES, R. N. LACEY, and PETER SMITH 940

206. Researches on Acetylenic Compounds. Part VIII. Miscellaneous Addition Reactions of Ethynyl Ketones.
By KENNETH BOWDEN, ERNEST A. BRAUDE, and E. R. H. JONES 945

207. Studies in Light Absorption. Part III. Auxochromic Properties and the Periodic System.
By KENNETH BOWDEN, ERNEST A. BRAUDE, and E. R. H. JONES 948

208. Researches on Acetylenic Compounds. Part IX. Heterocyclic Compounds derived from Ethynyl Ketones.
By KENNETH BOWDEN and E. R. H. JONES 953

209. Unsaturated Lactones. Part I. (Researches on Acetylenic Compounds. Part X.) A New Route to Growth-inhibitory αβ-Ethylenic γ- and δ-Lactones.
By L. J. HAYNES and E. R. H. JONES 954

210. The Synthesis of Analgesic Substances.
By J. A. BARLTROP 958

NOTES.—An Improved Method of Nitrating Aromatic *o*-Hydroxy-carboxylic Acids and their Esters.
By H. C. BARANY and M. PIANKA 965

Amides Derived from ω-Chloroacetophenone.
By WILLIAM A. WATERS 966

Synthesis of Acenaphthene. Part II.
By ALEXANDER SCHÖNBERG, RADWAN MOUBASHER, and AKILA MOSTAFA 966

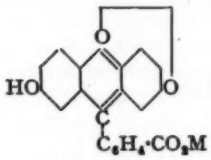
THE TILDEN LECTURE.—Substitution.
By E. D. HUGHES, D.Sc., PH.D., F.R.I.C. 968

THE RUTHERFORD MEMORIAL LECTURE.
By SIR HENRY TIZARD, K.C.B., F.R.S. 980

INDEX OF AUTHORS' NAMES.

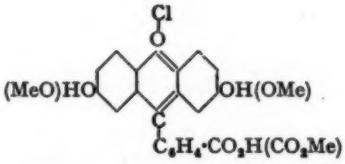
AXFORD, D. W. E., and Sugden, T. M., 901.
Barany, H. C., and Pianka, M., 965.
Barltrop, J. A., 958.
Bennett, G. M., Brand, J. C. D., and Williams, G., 869, 875.
Bowden, K., Braude, E. A., and Jones, E. R. H., 945, 948.
Bowden, K., and Jones, E. R. H., 953.
Brand, J. C. D., 880.
Brand, J. C. D. See also Bennett, G. M.
Braude, E. A. See Bowden, K.
Briggs, L. H., Openshaw, H. T., and Robinson, (Sir) R., 903.
Clemo, G. R., and Raper, R., 891.
Crooks, D. A., and Feetham, (Miss) F. M., 899.
Danby, C. J., Davoud, J. G., Everett, D. H., Hinshelwood, C. N., and Lodge, R. M., 918.
Davoud, J. G. See Danby, C. J.
Everett, D. H. See Danby, C. J.
Feetham, (Miss) F. M. See Crooks, D. A.
Hanby, W. E., and Rydon, H. N., 865.
Harper, S. H., 892.
Haynes, L. J., and Jones, E. R. H., 954.
Heilbron, (Sir) I., Jones, E. R. H., and O'Sullivan, D. G., 866.
Hinshelwood, C. N. See Danby, C. J.
Holmes, H. L., Openshaw, H. T., and Robinson, (Sir) R., 908, 910.
Howard, G. A., Kenner, G. W., Lythgoe, B., and Todd, A. R., 855, 861.
Hughes, E. D., 968.
Johnson, A. W., 895.
Jones, E. R. H., Lacey, R. N., and Smith, P., 940.
Jones, E. R. H., and Weedon, B. C. L., 937.
Jones, E. R. H. See also Bowden, K., Haynes, L. J., and Heilbron, (Sir) I.
Kenner, G. W., and Todd, A. R., 852.
Kenner, G. W. See also Howard, G. A.
Lacey, R. N. See Jones, E. R. H.
Lodge, R. M. See Danby, C. J.
Lythgoe, B. See Howard, G. A.
Mostafa, A. See Schönberg, A.
Moubasher, R. See Schönberg, A.
Openshaw, H. T., and Robinson, (Sir) R., 912.
Openshaw, H. T. See also Briggs, L. H., and Holmes, H. L.
O'Sullivan, D. G. See Heilbron, (Sir) I.
Petrow, V. A., 884, 888.
Pianka, M. See Barany, H. C.
Raper, R. See Clemo, G. R.
Robinson, (Sir) R. See Briggs, L. H., Holmes, H. L., and Openshaw, H. T.
Rydon, H. N. See Hanby, W. E.
Schönberg, A., Moubasher, R., and Mostafa, A., 966.
Smith, P. See Jones, E. R. H.
Solomon, W., 934.
Sugden, T. M. See Axford, D. W. E.
Tizard, (Sir) H., 980.
Todd, A. R. See Howard, G. A., and Kenner, G. W.
Waters, W. A., 966.
Weedon, B. C. L. See Jones, E. R. H.
Williams, G. See Bennett, G. M.

forward to explain the structure of the triphenylmethane dyes by E. and O. Fischer and by Nietzki, *i.e.*, that they are *p*-quinonoid. In the case of quinolphthalein, for which a *p*-quinonoid formula cannot be written, Green postulated an *o*-quinonoid, oxonium, structure, *i.e.* :

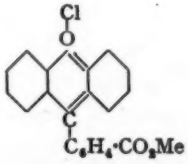


(coloured form)

These views found confirmation in the preparation and study of the ethers and esters of the phthaleins, and in the case of the quinolphthalein the oxonium idea found striking support in the discovery of the series of coloured chlorides (Green and King, *Ber.*, 1906, **39**, 2365; 1907, **40**, 3724. See also *J. Soc. Chem. Ind.*, 1908, **27**, 4; 1909, **28**, 638) :



Analogous oxonium chlorides (Green and King, *Ber.*, 1908, **41**, 3434) of the methyl esters of fluoran were also prepared in order to strengthen the case still further, *e.g.* :



Green made important contributions on the subject of aniline black, on both the chemical and technological sides. Although one of the oldest of dyestuffs, having been observed by Runge in 1834, and having been in industrial use since 1862, its constitution and the mechanism of its formation were unknown. There had, moreover, been no substantial change in the commercial production of aniline black, which takes place on the fibre through the oxidation of aniline hydrochloride, generally with sodium chlorate and a copper salt in the presence of heat and moisture (" ageing "), finishing off with a sodium dichromate bath. Variations of the process consist in the replacement of the copper salt by a ferrocyanide or by a vanadium salt. All these methods require great care to avoid damage to the cotton fibre, which could arise from the presence of hydrochloric acid or oxides of chlorine which could be formed under the conditions of the process. Green endeavoured to mitigate these defects by replacing chlorate oxidation by air oxidation, using a small quantity of *p*-phenylenediamine in the presence of a copper salt as the oxygen carrying system. This process was patented (B.PP. 16,189, 1907; 19,129, 1912) and was successfully reduced to practice by Green and P. F. Crosland in several well-known Continental dye works.

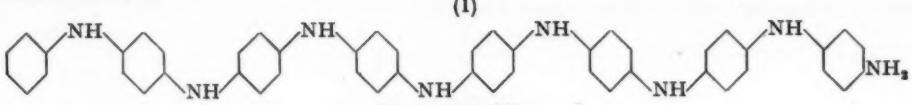
Green speculated, of course, on the rôle of the *p*-phenylenediamine in the new process (*J. Soc. Dyers and Col.*, 1909, **25**, 188) and was led to study the mechanism of the formation of aniline black. He differentiated between " ungreenable " aniline black, which is the end stage of the dyeing process, and products then undergoing investigation at the hands of Willstätter and his school which these workers thought to be aniline black (*Ber.*, 1909, **42**, 2147, 4118; 1910, **43**, 2976; 1911, **44**, 2162), but which in Green's view, merely represented intermediate stages to the formation of the true black. This led to controversy (Green and Woodhead, *J.*, 1910, **97**, 2388; 1912, **101**, 1117; *Ber.*, 1912, **45**, 1955; Green and Wolff, *Proc.*, 1912, **28**, 250; *Ber.*, 1911, **44**, 2570; 1913, **46**, 33; Green and Johnson, *Proc.*, 1913, **29**, 276; *Ber.*, 1912, **45**, 33; 1913, **46**, 3769), but eventually the work of Green's school substantiated his views by identifying the products of the stepwise, *in vitro*, oxidation of aniline with the successive stages in the production of the commercial black and thus establishing a plausible rationale of the process.

According to Green the first stage of the formation of aniline black consists in a series of oxidative additions of aniline to aniline in the manner of indamine formation (*i.e.*, linear) until eight aniline residues have been condensed.

Under carefully controlled conditions in the laboratory the products obtained from the oxidation of aniline salt by any of the commercial aniline black oxidation methods is either emeraldine or nigraniline, which substances are identical with the products well known to the aniline black dyer under these names. Emeraldine and nigraniline are merely oxidation stages of the same leuco compound which is the parent of all these substances,

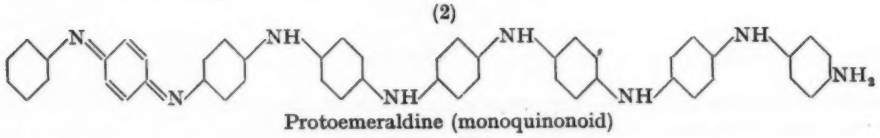
and also of two other oxidation stages which were discovered and named protoemeraldine and pernigraniline. The series is represented thus :

(1)



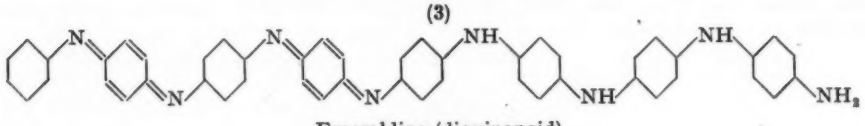
Leucoemeraldine

(2)



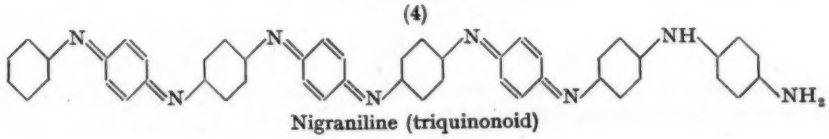
Protoemeraldine (monoquinonoid)

(3)



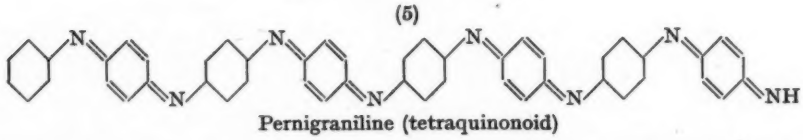
Emeraldine (diquinonoid)

(4)



Nigraniline (triquinonoid)

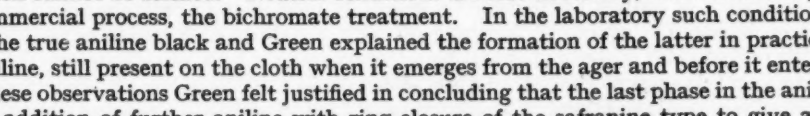
(5)



Pernigraniline (tetraquinonoid)

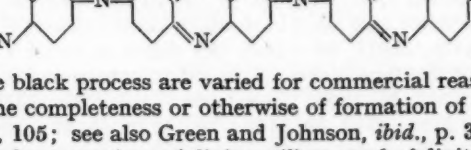
Degradation results from more drastic action and the molecule breaks down to quinone as would be expected from its linear structure.

From his chemical work and technological observations Green was able to demonstrate that the final stage in the formation of aniline black is of an entirely different type from those which precede it, which are pictured above. Free aniline is involved and without it the reaction cannot get beyond the nigraniline stage, *i.e.*, the ungreenable black cannot be formed. Neutral conditions are also necessary, such as in fact prevail in the last stage of the commercial process, the bichromate treatment. In the laboratory such conditions give a product identical with the true aniline black and Green explained the formation of the latter in practice as being due to residual free aniline, still present on the cloth when it emerges from the ager and before it enters the dichromate bath. From these observations Green felt justified in concluding that the last phase in the aniline black process is an oxidative addition of further aniline with ring closure of the safranine type to give a salt (usually the chromate) of the triphenylazoniumoctaphenazine :



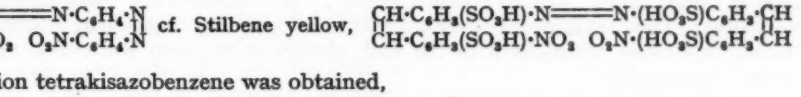
The conditions of the aniline black process are varied for commercial reasons and the degree of " ungreenability " attained depends on the completeness or otherwise of formation of the azine rings (Green and Wolff, *J. Soc. Dyers and Col.*, 1913, **29**, 105; see also Green and Johnson, *ibid.*, p. 338).

The similarity between the colour reactions of dinitrostilbene and of dinitroazobenzene, and the parallelism suggested by the formation of both substances by hypochlorite oxidations, thus :

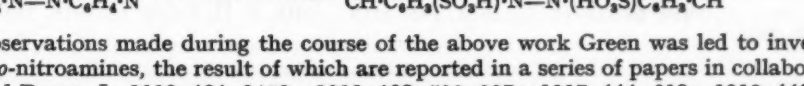


led Green to study the alkaline condensation of nitro-hydrazo compounds (Green and Bearder, *J.*, 1911, **99**, 1960; Green and Rowe, *J.*, 1912, **101**, 2003, 2443), with the object of finding further support for his views on

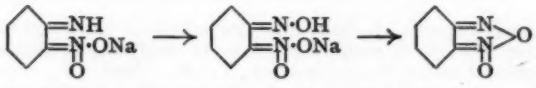
the mechanism of the formation of stilbene dyes. Just as the unstable intermediate products (4 : 4′-dinitrosostilbenes) in the formation of stilbene dyes show a deep bluish-red to blue colour in alkaline solution, so also does the partial reduction product of 4 : 4′-dinitroazobenzene. In both cases the alkaline solutions are readily decolourised by air oxidation, the former yielding dinitrostilbene, the latter dinitroazobenzene. Green's work confirmed the product obtained by reducing 4 : 4′-dinitroazobenzene with ammonium sulphide to be dinitrohydrazobenzene. This dissolves in strong alkali with an intense blue colour and in weak alkali with a violet blue colour. By acidifying the latter solution a compound was precipitated which, from analysis, appeared to be 4-nitro-4′-nitrosohydrazobenzene, $O_2N{\cdot}C_6H_4{\cdot}NH{\cdot}NH{\cdot}C_6H_4{\cdot}NO$, the coloured salts of which would have the quinonoid structure, $MO{\cdot}ON{:}C_6H_4{:}N{\cdot}N{:}C_6H_4{:}NOH$. While, therefore, the resemblance between the intermediate stages in the action of alkali on dinitrostilbene and on dinitroazobenzene is not complete, there is a striking analogy in the final product in the case of the dinitroazo compound, which yields bisnitrobenzeneazoazobenzene (dinitrotrisazobenzene) :



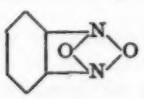
On alkaline reduction tetrakisazobenzene was obtained,



As the result of observations made during the course of the above work Green was led to investigate the oxidation products of *o*-nitroamines, the result of which are reported in a series of papers in collaboration with F. M. Rowe (Green and Rowe, *J.*, 1912, **101**, 2452; 1913, **103**, 508, 897; 1917, **111**, 613; 1918, **113**, 67, 2023; Green, B.P. 25,205, 1912). The behaviour of the nitroanilines with alkaline hypochlorite led Green to postulate the existence of quinonoid salts, of the nitronic acid type, *e.g.*, $C_6H_4{<}^{NH}_{NO_2Na}$, the reaction proceeding thus in the case of *o*-nitroaniline :



The resulting benz*iso*oxadiazole oxide (or benzfuroxan) was identical with the " dinitrosobenzene " of earlier literature. The constitution finally attributed was the symmetrical one :



because identical products were obtained from the pair of nitrotoluidines: $NH_2 : NO_2 : CH_3 = 1 : 2 : 5$ and $1 : 2 : 4$, and because of other supporting evidence.

Green's last published work in the dyestuffs field related to the so-called " sulphato dyes " and the " ionamines." The major bulk of textile dyeing is carried out in aqueous solution by means of dyestuffs which owe their solubility to the sulphonic acid group attached to an aromatic nucleus. (The sulphonation of rosaniline blue in 1862 by Nicholson was a crucial event in dyestuff history.) Green conceived the idea of solubilisation by means of an extra-nuclear sulphuric ester group and, in collaboration with Saunders, Adams, and Bate, made a series of new dyestuffs of the type $R{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_3H$ (R represents the rest of the chromophoric nucleus) which are conveniently and economically prepared by introducing the β-hydroxyethyl group into the dyestuff molecule (generally by reaction between an amino group and ethylene chlorohydrin), and then converting it to the sulphato compound by means of sulphuric acid (B.PP. 181,750, 182,031, 185,612, 186,878; Saunders, *J.*, 1922, **121**, 2667; Green and Saunders, *J. Soc. Dyers and Col.*, 1923, **39**, 39). This invention put a useful new weapon into the hands of the dyestuff chemist.

The sulphonic acid group, which plays such a useful rôle in conferring solubility on dyestuffs, has the drawback of enabling the dyeing process to be reversed under certain conditions, *e.g.*, washing with soap or alkali. A further complication arises from the behaviour of the rayon made from acetylcellulose, which has no affinity for dyes containing the SO_3H group, and thus presented a formidable problem to the dyer when it first appeared on the market. Green overcame these difficulties by attaching to a dyestuff devoid of solubilising groups a methyl-ω-sulphonic acid group, a process easily brought about by condensing formaldehyde-bisulphite with an amino group attached to the dyestuff nucleus. Dyes of this type, *i.e.*, $R{\cdot}NH{\cdot}CH_2{\cdot}SO_3H$, are easily soluble in water in the form of their salts, but, on penetrating the fibre, dissociate with loss of formaldehyde and bisulphite, the residual dyestuff, now no longer soluble in water, being left firmly attached to the fibre. When the dyestuff residue indicated by R in the above formula is suitably chosen, useful products for the dyeing of cellulose acetate rayon are obtained which appeared on the market under the name of " ionamines " (Green and Saunders, B.PP. 197,809, 200,873; Green, Saunders, and Frank, B.PP. 212,029, 212,030; Green and Saunders, *J. Soc. Dyers and Col.*, 1924, **40**, 138).

The above account of Green's experimental work covers the main topics which engaged his attention. Isolated researches * and the numerous lectures which he gave cannot be dealt with here, but the service he rendered to the dye technologist by his work on the identification of dyestuffs in substance and on the fibre should be recorded (Green, *J. Soc. Chem. Ind.*, 1893, **12**, 3; Green, Yeoman, and Jones, *J. Soc. Dyers and Col.*, 1905, **21**, 236; Green and Stephens, *ibid.*, 1907, **23**, 118; Green, Yeoman, Jones, Stephens, and Haley, *ibid.*, p. 252; Green and Frank, *ibid.*, 1910, **27**, 83). This work, extending over a number of years, was eventually published in book form. In spite of the volume of his writing on scientific, technological and economic matters, Green was only responsible for one other book, the *Systematic Survey of the Organic Colouring Matters*, adapted from Schultz and Julius's *Farbstofftabellen*, and incorporating a useful synopsis of information on the principal intermediates (published 1894).

The words of Thomas Browne, quoted at the beginning of this notice, are particularly appropriate to our subject. Green's " pure flame " was his creative genius; his " invisible fire " was his extraordinary faith in the urgency of his cause. They sustained a comparatively frail body through a long life, full to the last of fruitful activity. He saw his cause triumphant in the end, though it required the ordeal of war to bring it home reluctantly to his countrymen.

J. Baddiley.

* Examples are found in the following references: *Ber.*, 1893, **26**, 2772; (with A. G. Perkin) *J.*, 1906, **89**, 1811; (with R. N. Sen) *J.*, 1910, **97**, 2242; *J.*, 1912, **101**, 1113; (with K. H. Vakil) *J.*, 1918, **113**, 35; (with F. M. Rowe) *J.*, 1918, **113**, 955.

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183. *Experiments on the Synthesis of Purine Nucleosides. Part XIII. An Improved Method for the Cyclisation of 4-Glycosidamino-5-thioformamidopyrimidines.*

By G. W. Kenner and A. R. Todd.

As anticipated on theoretical grounds alcoholic alkoxide solutions have proved effective reagents for the cyclisation of 4-glycosidamino-5-thioformamidopyrimidines to 9-glycosidopurines. Both 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine (I; R = MeS; R_1 = *d*-xylosido) and its triacetyl derivative (I ; R = MeS; R_1 = triacetyl-*d*-xylosido) give exclusively 9-*d*-xylopyranosido-2-methylthioadenine by this method, whereas the triacetyl derivative heated with a mixture of potassium acetate and acetic acid in methyl cyanide solution gives 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine. The results obtained with acetylated compounds are interpreted in terms of a chelation hypothesis.

The cyclisation of 4-amino-5-thioformamidopyrimidines to yield purine derivatives, first observed by Todd, Bergel, and Karimullah (*J.*, 1936, 1557) was extended by Baddiley, Lythgoe, McNeil, and Todd (Part I; *J.*, 1943, 383) and utilised for the synthesis of 9-alkylpurines in excellent yield. In subsequent papers of this series (Parts VI, IX, X, XI; *J.*, 1944, 318, 652, 657; 1945, 556) analogous syntheses of 9-glycosidopurines have been effected by cyclisation of 4-glycosidamino-5-thioformamidopyrimidines in boiling pyridine solution. In this important field, however, the yields obtained were frequently low and isolation of the products was complicated by extensive decomposition during the reaction. These defects in the final stage of the method were especially serious in studies now in progress on the synthesis of 9-glycofuranosidoadenines where the pyrimidine intermediates were likely to be at once less accessible and less stable than those employed in the syntheses of 9-glycopyranosidoadenines already described. Accordingly the cyclisation procedure has been re-examined with the object of practical improvement.

We consider that the mechanism of the cyclisation reaction is satisfactorily represented by Scheme I. In it the function of the base *B* in promoting the initial prototropic change and the final ring-closure was presumably fulfilled in earlier experiments (*loc. cit.*) by the solvent employed (water, pyridine, quinoline). It appeared noteworthy that Howard, Lythgoe, and Todd (Part XI; *loc. cit.*) observed ready cyclisation of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine * in aqueous alkali, although considerable quantities of the corresponding 5-formamido-compound were simultaneously formed. It was therefore expected that the use of alcoholic sodium alkoxide solutions as cyclisation media might prove successful, and this was borne out by experiment; cyclisation of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine by this method proceeded smoothly giving 9-*d*-xylopyranosido-2-methylthioadenine. From a series of experiments using methanol, ethanol, and *n*-propanol it appeared that best results were obtained by refluxing the thioformamido-compound in ethanol with one mol. of sodium alkoxide. Under these conditions the thioformamido-compound dissolved slowly and yields of *ca.* 63% were obtained; if the amount of alkoxide was increased immediate dissolution of the thioformamido-compound occurred but the yield of product was somewhat lower. Reactions in *iso*propanol and *tert.*-butanol were accompanied by considerable darkening and were less successful. A point of interest in these experiments is that, although

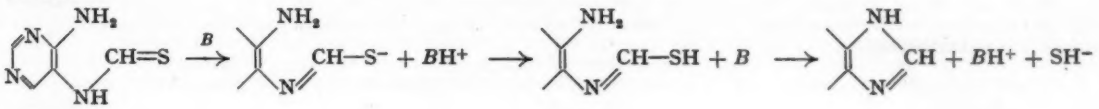
* In previous papers of this series the term pyranoside has been applied only to glycosides in which the lactol ring structure has been rigidly established. In view of the virtual certainty of the ring-structure of this and other pyrimidine glycosides mentioned in this paper and to avoid confusion in later recording studies on furanosides we have assumed the pyranoside structure in naming them.

in one case a small amount of 6-amino-4-*d*-xylopyranosidamino-5-formamido-2-methylthiopyrimidine was formed as a by-product, no 6-*d*-xylopyranosidamino-2-methylthiopurine was ever isolated.

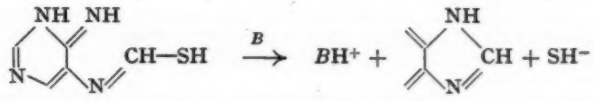
Baddiley, Lythgoe, and Todd (Part VI; *loc. cit.*) prepared 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (I; R = Me; R_1 = *d*-xylosido) but were unable to cyclise it by boiling it in pyridine solution; the corresponding triacetyl compound (I; R = Me; R_1 = triacetyl-*d*-xylosido), however, yielded, under similar conditions, a mixture of 9-triacetyl-*d*-xylopyranosido-2-methyladenine (II; R = Me, R_1 = triacetyl-*d*-xylosido) and 6-triacetyl-*d*-xylopyranosidamino-2-methylpurine (III; R = Me; R_1 = triacetyl-*d*-xylosido) in moderate yield. Application of the alkoxide method to (I; R = Me; R_1 = *d*-xylosido) gave the 9-substituted purine (II; R = Me; R_1 = *d*-xylosido) in a yield of *ca.* 20% while the same product was obtained in 63% yield by heating the corresponding triacetyl derivative with 1 mol. of sodium methoxide in ethanol under anhydrous conditions. The preparation of 9-*d*-xylopyranosidoadenine and 9-*d*-ribopyranosidoadenine from the appropriate triacetylthioformamido-compounds was effected with equal ease. Whether the low yield in the case of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine is to be ascribed to the low solubility of this compound or to a structural difference from the product of deacetylation of 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine is not at present clear.

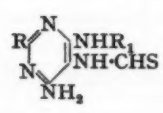
In none of the above experiments was any 6-glycosidaminopurine obtained, in contrast to the general production of such compounds when acetylated thioformamidoglycosides are cyclised by heating in pyridine solution. Since deacetylation is very rapid in hot sodium alkoxide solution (Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613) all the experiments with acetylated glycosides should be regarded as effectively ring-closures of acetyl-free glycosides; indeed, the behaviour of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine in ethanolic sodium methoxide is indistinguishable from that of its triacetyl derivative. The present results are thus in agreement with the observation recorded in Part XI (*loc. cit.*) that no 6-glycosidaminopurine is obtained on cyclising 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine and with the views expressed in Part I (*loc. cit.*), where it was shown that almost quantitative yields of 2 : 9-dimethyladenine and 2-methylthio-9-methyladenine are obtained, to the exclusion of the 6-methylaminopurines, by cyclising the corresponding 6-amino-4-methylamino-5-thioformamidopyrimidines. It was suggested that such thioformamido-compounds exist in form (IV) rather than (V), and it was implied that ring-closure occurred by the mechanism shown in Scheme 1 and not by that in Scheme 2, which involves the intervention of an imino-group and elimination of a proton from elsewhere in the molecule.

Scheme 1 :

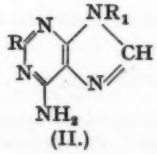


Scheme 2 :

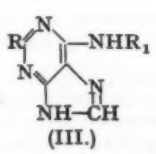




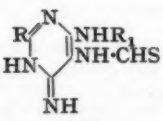
(I.)



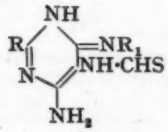
(II.)



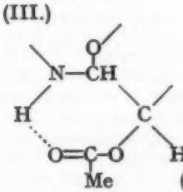
(III.)



(IV.)



(V.)



(VI.)

These considerations naturally require exclusive formation of 9-alkylpurines and, by analogy, 9-glycosidopurines when compounds of type I are cyclised. By employing base catalysis under conditions which nevertheless avoided deacetylation, we have been able to confirm that acetylation of the sugar residue alters this situation. Treatment of 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine (I; R = MeS; R_1 = triacetyl-*d*-xylosido) with 4 mols. of potassium acetate and 2 mols. of acetic acid in boiling anhydrous methyl cyanide gave a substantial yield of 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (III; R = MeS; R_1 = triacetyl-*d*-xylosido). Under similar conditions 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamidopyrimidine (I; R = H; R_1 = triacetyl-*d*-xylosido) was much less reactive and gave only a small amount of 9-*d*-xylopyranosidoadenine; the yield of cyclised material was too low to permit of isolation of any 6-glycoside which might have been formed. Accordingly we feel justified in reiterating the hypothesis briefly mentioned in Parts IX and XI of this series (*locc. cit.*) that a chelate ring may

be formed, as shown in (VI), through a hydrogen bond between the 2'-acetyl group in the sugar residue and the hydrogen atom of the glycosidic NH-group—a sterically feasible structure. The effect of such chelation would be to induce negative charge on the glycosidic nitrogen atom thus increasing the basicity of that atom and also, indirectly, of the 6-imino-group. As a result, the reactivity of the whole molecule in the cyclisation process would be increased and the production of 6-triacetylglycosidopurines according to Scheme 2 would be possible. Increased general reactivity in such compounds is indicated by the shorter period of heating necessary for the cyclisation of the acetylated thioformamidoglycosides in pyridine solution and by the production of considerable quantities of 9-glycosidopurines in such reactions. Explanations resting on simple steric considerations are, in our view, much less satisfactory. The question of the balance between 6- and 9-glycoside formation in individual cases is not easy to determine owing to the difficulty of quantitative isolation of reaction products.

Two other points emerge from the present work, one of theoretical and the other of practical interest. It is clear that ring-closure of the thioformamido-compounds is most rapid in those containing a 2-methylthio-substituent. The increased basicity of the 4(6)-amino group so indicated is reflected in the relatively easy glycosidisation of 4 : 6-diamino-2-methylthiopyrimidine (Baddiley, Lythgoe, and Todd, Part III; *J.*, 1943, 571) whilst a similar ease of nitrosation (Lythgoe, Todd, and Topham, Part V; *J.*, 1944, 315) is evidence of simultaneously increased electron density at C_5 in the pyrimidine nucleus. Apparently the pyrimidine ring system transmits electronic disturbance efficiently to both the 5- and the 4 : 6-positions in contrast to the *o*-*p*-selectivity displayed in benzenoid compounds.

In the course of preparative work acetylated thioformamidoglycosides are frequently obtained as gels which offer considerable (at times insuperable) resistance to direct crystallisation. The rough chromatographic purification technique described in the experimental portion is an effective method of overcoming this difficulty and is thus a useful complement to the improved cyclisation procedure in synthesising purine glycosides.

Experimental.

The m. ps. of certain purine glycosides prepared by the methods given below are somewhat higher than those recorded for materials prepared by cyclisation in pyridine solution. It has been noted in previous work that these m. ps., all accompanied by decomposition, whilst reproducible with any given specimen, vary somewhat in different preparations without noticeable alteration in analytical composition or purity.

9-d-*Xylopyranosido*-2-*methylthioadenine from* 6-*Amino*-4-d-*xylopyranosidamino*-5-*thioformamido*-2-*methylthiopyrimidine*.—(1) The thioformamido-compound (100 mg.) and sodium methoxide (16 mg.; 1 mol.) were heated in boiling methanol (5 c.c.) during 5 hours. Evaporation under reduced pressure and trituration of the residue in water gave 9-*d*-xylopyranosido-2-methylthioadenine, m. p. 293—294° (yield, 45%). The results obtained in a series of experiments are tabulated below.

Solvent.	Mols. of sodium methoxide.	Time (hours).	Yield of 9-xyloside (%).
Methanol	1	5	45
Methanol	2	5	44 *
Ethanol	1	6	63
Ethanol	2	3½	58
Ethanol	4	2	23
n-Propanol	1	2	49
*iso*Propanol	1	4	30

* The aqueous filtrate neutralised and concentrated to small bulk slowly deposited 6-amino-4-*d*-xylopyranosidamino-5-formamido-2-methylthiopyrimidine (*ca.* 2%).

When the thioformamido-glycoside was heated with sodium *tert.*-butoxide in *tert.*-butanol, severe decomposition occurred and no purine glycoside could be isolated.

Cyclisation Experiments with 6-*Amino*-4-*triacetyl*-d-*xylopyranosidamino*-5-*thioformamido*-2-*methylthiopyrimidine*.—(1) The acetylated thioformamido-compound (200 mg.) was refluxed in methanol (10 c.c.) with sodium methoxide (100 mg.; 4·2 mols.) during 6 hours. On allowing to cool, colourless needles of 9-*d*-xylopyranosido-2-methylthiopyrimidine (45 mg.) separated; a further amount (5 mg.) was obtained from the mother liquors which, however, contained no 6-*d*-xylopyranosidamino-2-methylthiopurine.

(2) The solution of the acetylated thioformamido-compound (100 mg.), anhydrous potassium acetate (81 mg.; 4 mols.), and acetic acid (0·025 c.c.; 2 mols.) in anhydrous methyl cyanide (5 c.c.) was heated under reflux for 4 hours. Potassium acetate separated on cooling and was filtered off. The filtrate was evaporated under reduced pressure and the residue triturated with ethanol (3 c.c.) giving colourless needles of 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (21 mg.), m. p. and mixed m. p. 251—252°. The alcoholic mother liquor contained a further small amount of the same product which was isolated, after hydrolysis with methanolic ammonia, as 6-*d*-xylopyranosidamino-2-methylthiopurine, m. p. and mixed m. p. 225—226° (total yield, 33%).

9-d-*Xylopyranosido*-2-*methyladenine*.—(1) 6-Amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (50 mg.) and sodium methoxide (4·5 mg.; 1 mol.) were heated under reflux in methanol (5 c.c.) for 8½ hours. Unchanged starting material (15 mg.) separated on cooling, and from the solution 9-*d*-xylopyranosido-2-methyladenine (5 mg.) was isolated by evaporation and trituration with water (yield, allowing for recovered material, 16%). A second experiment using *n*-propanol as solvent in place of methanol gave the same product in 19% yield, and a third using 2 mols. of sodium methoxide in ethanol gave a yield of 11%.

(2) Anhydrous 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (100 mg.) and sodium methoxide (12·5 mg.; 1 mol.) were refluxed in ethanol (7 c.c.) in an atmosphere of nitrogen. A crystalline solid gradually separated and evolution of hydrogen sulphide had ceased after 4 hours. The mixture was left overnight and the 9-*d*-xylopyranosido-2-methyladenine, m. p. 291—292°, which had separated, was collected (yield, 63%). No evidence for the presence of the corresponding 6-xyloside was obtained.

In exactly similar fashion, 9-*d*-xylopyranosidoadenine (67%; m. p. 303—304°) and 9-*d*-ribopyranosidoadenine (51%; m. p. 252°) were prepared from the appropriate acetylated thioformamido-compounds.

Purification of 6-*Amino*-4-*triacetyl*-d-*xylopyranosidamino*-5-*thioformamidopyrimidine*.—A solution of the crude resinous thioformamido-compound (from 1·0 g. of the corresponding acetylated azo-compound, Part IX, *loc. cit.*) in ethyl acetate (25 c.c.) was adsorbed on neutral alumina (30 g., column 2·5 cm. diam.) and the column washed with ethyl acetate (50 c.c.) and then with chloroform (50 c.c.). Elution with pyridine (50 c.c.) gave the thioformamido-compound (500 mg.) which crystallised readily from ethanol in colourless needles.

The same technique has been applied successfully to a number of other acetylated thioformamido-glycosides.

We are grateful to the Department of Scientific and Industrial Research for a Senior Award held by one of us (G. W. K.) and to Roche Products Limited and Imperial Chemical Industries Limited for grants and gifts of chemicals.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 28th,* 1946.]

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184. *Experiments on the Synthesis of Purine Nucleosides. Part XIV. An Interpretation of Some Interconversion Reactions of* N-*Glycosides.*

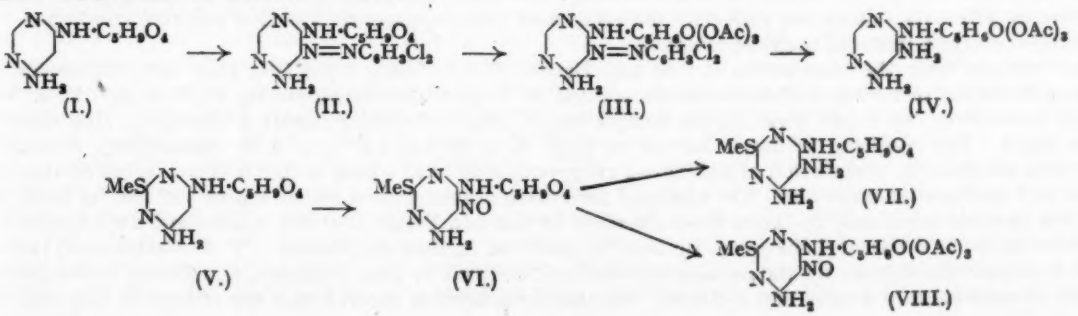
By G. A. HOWARD, G. W. KENNER, B. LYTHGOE, and A. R. TODD.

Reinvestigation of the anilineribosides described in recent patent specifications (Lee *et al.* of Hoffmann-La Roche Inc., U.S.PP. 1945, 2,384,102—2,384.104) has provided for the first time clear evidence of the occurrence in the *N*-glycoside series of furanoside ⇄ pyranoside changes. Aniline-*d*-ribopyranoside is isomerised by boiling in alcohol to aniline-*d*-ribofuranoside. Aniline-α-*d*-ribofuranoside is partially converted in moist pyridine into the β-isomer without change in lactol ring structure, but in pyridine containing acidic catalysts it gives an equilibrium mixture of the α- and β-pyranosides. The bearing of these findings on the problem of the lactol ring structure of the 6-amino-4-*d*-xylosidaminopyrimidine derivatives described in Parts IX and XI (*J.*, 1944, 652; 1945, 556) is discussed; consideration of all the relevant evidence strongly favours the view already expressed, *viz.*, that they all possess, like the 9-*d*-xylosidopurines into which they can be converted, the pyranoside structure. The isomerism existing between xylosides of Series I and Series II (*loc. cit.*) is therefore of the αβ-type.

In terms of this view a reasonable interpretation is provided of the remarkable changes described in Parts IX and XI (*locc. cit.*) when only one form of a 4-*d*-xylosidaminopyrimidine derivative is produced from each of two isomers. It is suggested that xylosides of the latter type (*i.e.*, those existing in two stable forms) fail to show αβ-interconversion because the velocity of such change is too small, whilst in xylosides of the former type (*i.e.*, those isolable in only one stable form) αβ-interconversion is easy, but the equilibrium concentration of one of the forms is too small to permit its isolation; the interconversion reactions are therefore best regarded as mutarotations. In considering the influence of the structure of a 4-*d*-xylosidaminopyrimidine derivative in determining the ease of its mutarotational change, and hence in deciding to which of the above types a xyloside shall belong, it is pointed out that the determining factor appears to be the electron availability at the atom attached glycosidically to C_1 of the sugar residue, and the way in which this factor is affected by the presence of different substituents in the pyrimidine nucleus and by acetylation of the hydroxyls of the sugar residue is discussed.

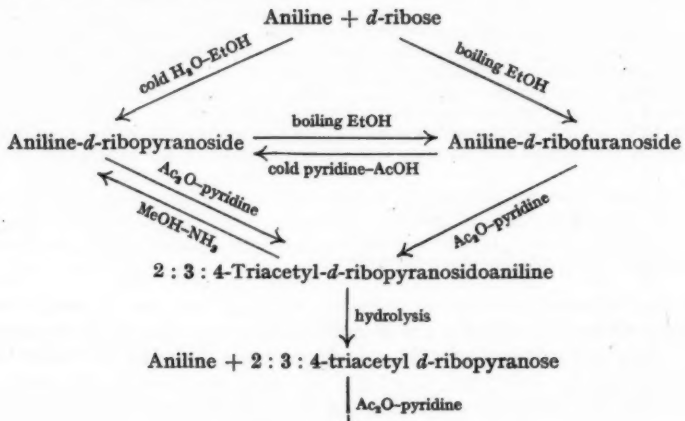
In compounds where isomerisations both of the αβ-type and of the closely related furanoside ⇄ pyranoside type are theoretically possible, some factors affecting the relative velocities of the two changes are considered, and the behaviour of aniline-α-*d*-ribofuranoside is shown to be in harmony with mechanisms proposed for mutarotational changes in *O*- and *N*-sugar derivatives.

CERTAIN 6-amino-4-glycosidaminopyrimidine derivatives prepared by the method described in Part III (*J.*, 1943, 571) have been shown to display an isomerism the seat of which is the sugar residue (Parts IX and XI, *loc. cit.*); thus 6-amino-4-*d*-xylosidaminopyrimidine (I) and its 2-methylthio-derivative (V) each appear to exist in two forms, only one of which in each case has so far been obtained crystalline. The two forms of (I) can be converted into well-defined isomeric 5-arylazo-derivatives (II) and triacetyl-5-arylazo-derivatives (III); both isomers of (III) give on catalytic reduction the same triacetyl-5-amino-derivative (IV). Similarly the two forms of (V) yield isomeric 5-nitroso-derivatives (VI), reduction or acetylation of which is accompanied by loss of isomerism to give only one form of the 5-amino-derivative (VII) or the triacetyl-5-nitroso-derivative (VIII). On account of its possible importance for the chemistry of the *N*-glycosides some explanation of these remarkable reactions seems called for, since they do not appear at first sight to find any parallels in the *O*-glycoside series. The present paper provides an interpretation of these changes, together with an account of some closely related reactions which we have observed amongst the simpler *N*-glycosides of aromatic amines.



General experience of sugar chemistry suggested the provisional view expressed in Part XI (*loc. cit.*) that the isomerism was of the αβ-type and that the 4-*d*-xylosidaminopyrimidines possess a pyranoside structure; this structure has been established for the 9-*d*-xylosidopurine derivatives into which they can be converted, but rigid proof for the *d*-xylosidaminopyrimidines by a direct determination of the ring structures of both members of an isomeric pair has not so far been obtained. It might therefore be argued that at least one member of such a pair might be a furanoside, particularly if any weight were to be attached to the claim of Kuhn and Ströbele (*Ber.*, 1937, **70**, 773) that such a structure is present in their *o*-nitroanilinepentosides, which show a striking formal similarity to our 4-glycosidaminopyrimidines and are produced under identical reaction conditions. The grounds on which these authors base their claim, however (formation of trityl derivatives), are known to be insecure, and in some experiments to clarify this point it has been found in this laboratory (with Mr. N. W. Bristow) that at least one of the pentosides of the Heidelberg workers (*viz.*, *o*-nitroaniline-*l*-arabinoside, the only compound so far investigated) is in fact a pyranoside; these investigations will be described in a later paper.

The *o*-nitroanilinepentosides therefore provide no support for the view that the method described in Part III (*loc. cit.*) gives rise to furanosides. That such structures may sometimes be obtained by condensation of amines with pentoses is clear from recent patent specifications of Hoffmann–La Roche, Inc., which have attracted our attention on these and other grounds. Lee, Solmssen, and Berger (U.S.P. 1945, 2,384,102) described a method of condensing aromatic amines and pentoses in aqueous alcoholic solution at room temperature and pH *ca.* 4 to give *N*-pentosides to which the pyranoside structure was ascribed, and showed that in many cases condensation of the components by refluxing their alcoholic solutions yielded isomeric *N*-pentosides which they considered to be furanosides. The mutarotation behaviour of these isomeric pentosides shows that the isomerism is not due to αβ-differences, but no convincing proof was presented of the correctness of the lactol ring structures ascribed, and the results contrast strikingly with those obtained in the formation of *O*-glycosides where methanolic hydrogen chloride is known to react with aldoses in the cold to give furanosides, and at higher temperatures to give pyranosides. In view of this, and of possible applications of the methods described to the production of 4-glycosidaminopyrimidine derivatives, we have reinvestigated and extended some of the work of the American authors.



We found that, as they reported, aniline and *d*-ribose condense in the cold to give aniline-α-*d*-ribopyranoside; the isomeric aniline-α-*d*-ribofuranoside we obtained both by direct condensation of the components in boiling alcohol and by isomerisation of the pyranoside in the same solvent. We observed that mutarotation of both isomerides was arrested in dry pyridine, and took place only after addition of a small quantity of water; further, it appears that isomerisation of the pyranoside to the furanoside in boiling alcohol is dependent upon some factor(s) as yet unknown, since although we were sometimes successful in effecting the change, in other experiments, conducted with pure materials and under apparently identical reaction conditions, only unchanged starting material could be isolated.

In contrast with the statements of Lee and Berger (U.S.P. 1945, 2,384,104) that both furanoside and pyranoside forms of aniline-*d*-riboside can be acetylated to give the corresponding 2 : 3 : 5- and 2 : 3 : 4-triacetyl derivatives, we found that during acetylation of aniline-*d*-ribofuranoside a change in ring structure takes place. The resulting triacetyl derivative, $[\alpha]_D^{18°} = +30{\cdot}7 \pm 1{\cdot}3°$ ($c = 4$ in chloroform), is identical with that obtained by acetylation of aniline-α-*d*-ribopyranoside, into which in fact it is converted by deacetylation with methanolic ammonia. The triacetyl derivative obtained from either source yielded, on hydrolysis with hot aqueous acetic acid by the method described by Lee and Berger (*loc. cit.*), aniline and a syrupy product identified as 2 : 3 : 4-triacetyl ribopyranose since it yields on further acetylation 1 : 2 : 3 : 4-tetra-acetyl ribose; these facts provide support for the pyranoside structure ascribed by Lee, Solmssen, and Berger to the product of cold condensation of aniline and *d*-ribose. Further investigation showed that the change in ring structure

which occurs during the acetylation of aniline-α-*d*-ribofuranoside is due to the rapid conversion of this compound into the isomeric pyranoside which takes place in pyridine in presence of acids (*e.g.*, acetic acid); the mutarotation curve of the furanoside in such solutions shows an end value identical with that of the pyranoside in moist pyridine or in pyridine containing acetic acid. These changes are summarised in the scheme on opposite page.

They provide what we believe to be the first clear evidence of the occurrence in *N*-glycosides of changes in lactol ring structure, although it seems probable that the behaviour of the aniline glucosides studied by Irvine and Gilmour (*J.*, 1908, **93**, 1429), and believed by them to be due to αβ-isomerisation, is really to be ascribed to changes in ring structure analogous to those described above for the aniline ribosides. They obtained by cold condensation of the compounds a *d*-glucosidoaniline, $[\alpha]_D = +10{\cdot}7°$ (probably a furanoside), which in methanol at room temperatures underwent conversion (strongly catalysed by acids) into a more stable form, $[\alpha]_D = -52{\cdot}3°$ (probably a pyranoside), the change being partially reversed on refluxing the latter in methanol. Such alterations in ring structure are of course known to occur in *O*-glycosides, *e.g.*, in the conversion of methyl-*d*-ribopyranoside into 1 : 2-monoacetone methyl-*d*-ribofuranoside (Levene and Stiller, *J. Biol. Chem.*, 1934, **106**, 421); the acid catalysed isomerisations of both α- and β-forms of 3 : 6-anhydro-methyl-*d*-glucopyranoside into the corresponding furanoside derivatives, discovered by Haworth, Owen, and Smith (*J.*, 1941, 88), and shown by them to be possible because of the considerable strain existing in the 1 : 5-lactol ring, provide particularly interesting examples.

The demonstration that in many cases condensation of an amine and a pentose at room temperature gives a pyranoside whereas condensation in boiling alcohol gives the furanoside prompts the question as to whether such a distinction is of general validity, since if it were some doubt might be cast on the pyranoside nature of the products obtained by the method described in Part III (*loc. cit.*). We have found, however, that there is often no such distinction, even where aromatic amines are used. Thus aniline and *d*-xylose gave the same aniline-*d*-xyloside by both methods of condensation, and in the course of other work in this laboratory a similar finding has been made for *o*-nitroaniline and *d*-ribose. Neither 4 : 6-diaminopyrimidine nor its more reactive 2-methylthio-derivative could be brought into reaction with *d*-ribose under the conditions of cold condensation described by Lee, Solmssen, and Berger (*loc. cit.*). These results offer no opposition to the view that, especially in the case of weakly basic amines such as the derivatives of *o*-nitroaniline and 4 : 6-diaminopyrimidine, condensation in hot alcohol in presence of acidic catalysts may give rise completely or almost completely to pentopyranosides. That our 6-amino-4-*d*-xylosidaminopyrimidine derivatives do in all probability possess this structure is supported by the following considerations. If, for example, one of the isomers of the triacetyl-5-arylazo-derivative (III) were a furanoside, it would follow that during catalytic hydrogenation to the triacetyl-5-amino-derivative (IV) simultaneous migration of an acetyl group and change in lactol ring structure takes place. Migration of acetyl groups in partly substituted sugar compounds is known to occur occasionally, and the behaviour of the aniline ribosides described above shows that furanose–pyranose changes in *N*-glycosides cannot be considered as excluded, but a transformation of this type, where both glycosidic centre and all hydroxyl groups capable of providing alternative positions for ring closure are blocked by substitution, is quite without parallel and seems to us most unlikely. Moreover it will be shown in another paper that the relevant optical data are in accord with the view that members of an isomeric pair of 4-*d*-xylosidaminopyrimidine derivatives stand in αβ relationship to each other.

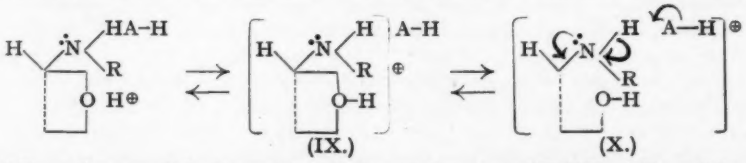
In terms of this view, we suggest that those reactions of our 4-*d*-xylosidaminopyrimidine derivatives in which only one isomer is produced from each of two different isomers are best interpreted as involving interconversion reactions of essentially the same sort as those concerned in mutarotations; specifically, that the acetylation of 5-nitroso-6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine-II (VI) to give 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-I (VIII) (Part XI, *loc. cit.*) is to be regarded as due to the tendency of the unknown 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-II first produced in the reaction to undergo a facile and complete mutarotation to its αβ-isomer. Since mutarotation in the sense of an observable change in rotation due to equilibration of α- and β-forms has not hitherto been recorded for any of our glycosidaminopyrimidine derivatives, an initial difficulty may attach to this conception. This is resolved on realisation that constitutional features may decide in two ways whether a sugar derivative shall exhibit mutarotation in the strict sense, either by affecting the velocity with which αβ-change takes place or by controlling the final position of the equilibrium between the two forms. The two forms of *o*-nitroxylidine-*l*-arabinoside (Kuhn and Ströbele, *loc. cit.*) are presumably compounds where the velocity of αβ-change is too low to be measurable under ordinary conditions; examples of the opposite type are α-acetochloroglucose and tetra-acetyl-*d*-glucosido-*p*-toluidine, which show no mutarotation in the accepted sense because each represents the more stable member of a pair of compounds of widely differing stabilities. That compounds of these structures are capable of αβ-isomeric change is shown by the behaviour of their αβ-isomers, which on dissolution in alcohol undergo rapid and virtually complete αβ-change (Schlubach and Gilbert, *Ber.*, 1930, **63**, 2292; Kuhn and Dansi, *Ber.*, 1936, **69**, 1745). We suggest that the 4-*d*-xylosidaminopyrimidine derivatives existing in isomeric forms, *e.g.*, (I), (II), (III), (V), and (VI), show no mutarotation because the velocity of αβ-change is too small, and that in derivatives of structures (IV), (VII), and (VIII) αβ-change is facile, but because the two possible forms are of widely differing stabilities the equilibrium mixture obtained contains no isolable quantity of the less stable form. What structural features are responsible for this disparity in the stabilities of two αβ-isomers, and how these determine, for example, that in the acetohalogeno-

sugars it is usually the α-form which is the more stable, whilst in the 5 : 6-diamino-4-glycosidaminopyrimidines it is, as will be shown in a further paper, the β-form which is usually the more stable, are questions to which at present no answer can be given. It is, however, possible in the light of what is already known of the influence of structural features on ease of mutarotational changes to understand why compounds of structures (IV), (VII), and (VIII) show, in contrast to the other xylosidaminopyrimidines, the high tendency to αβ-changes which causes them to appear in only a single form.

Kuhn and Birkofer (*Ber.*, 1938, **71**, 1535) have investigated the mutarotation of secondary (NHR–sugar) and tertiary (NR_1R_2–sugar) *N*-glycosides in its relationship to the Amadori rearrangement and to the capacity of such compounds to undergo reduction to *N*-substituted 1-aminosugar alcohols. Their results show that some tertiary *N*-glycosides may undergo mutarotation, that such changes are of the acid-catalysed variety, and that they are difficult or impossible in the glycosides of weakly basic compounds (*e.g.*, theophylline) and increasingly facile in those of the more strongly basic compounds (*e.g.*, dibenzylamine and piperidine). Parallel changes to those of the tertiary *N*-glycosides occur in some *O*-glycosides but are in general less facile, presumably because of the weaker basicity of the aglycone; examples are the isomerisation of tetra-acetyl β-methylglucoside (Pacsu, *Ber.*, 1928, **61**, 137, 1513) which takes place in boiling chloroform and requires the presence of a powerful electrophilic catalyst (*e.g.*, titanium tetrachloride), and the acid catalysed changes of 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucoside (Haworth, Owen, and Smith, *loc. cit.*) and the corresponding galactoside (Haworth, Jackson, and Smith, *J.*, 1940, 620) to their β-isomers, changes promoted by the existence of strain in the lactol ring.

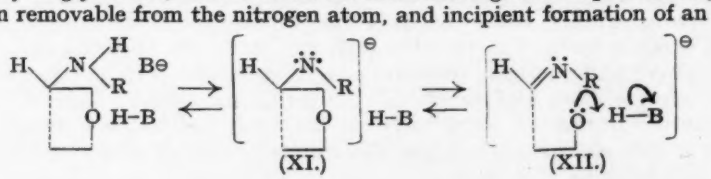
In the case of secondary *N*-glycosides, quantitative measurements have been made by Baker of the velocities of rotational change occurring in *p*-substituted anilides of tetra-acetyl glucose (*J.*, 1928, 1583) and tetramethyl glucose (*J.*, 1928, 1979); he found that in presence of acid the observed velocities ran parallel with basicity of the aglycones. In a later paper (*J.*, 1929, 1205) Baker was unable to detect mutarotation in tetra-acetyl glucosides of some secondary amines and concluded that for mutarotation due to αβ-change to take place "the original sugar derivative itself, as distinct from its cation must contain a separable hydrogen atom." Work already cited has shown that this conclusion is no longer tenable, and some reservations may be necessary regarding his interpretation of the earlier results, since, as will be shown later, complicating factors may be at work in acetylated secondary *N*-glycosides, and since the evidence given does not establish definitely that the changes in rotation observed by Baker were due completely to αβ-isomerisation. However this may be, sufficient qualitative data are available for sugar derivatives with unsubstituted alcoholic hydroxyl groups to show the broad general influence of the basicity of a group OH or NHR attached to the glycosidic centre on the facility with which mutarotation takes place. In such compounds basic catalysis of the mutarotation is possible and, where a free hydroxyl group is present at C_1, represents the main pathway of the change; in the secondary *N*-glycosides this mechanism appears to be somewhat less effective, but the acid-catalysed mechanism is very much more effective than for the oxygen analogues, and becomes increasingly so with more strongly basic aglycones; thus although many of the *N*-glycosides of aniline, *p*-toluidine, and *p*-phenetidine are known to mutarotate, such changes have not been observed in the more feebly basic *o*-nitroaniline derivatives.

These results are consistent with mechanisms of the type proposed for *d*-glucose by Fredenhagen and Bonhoeffer (*Z. physikal. Chem.*, 1938, *A*, **181**, 392) whose views are essentially similar to those expressed by Lowry (*J.*, 1925, **127**, 1371). For *N*-glycosides, the acid catalysed change, although doubtless a continuous process, may be considered in two stages, the first involving attack on the lactol ring oxygen atom by a proton



(IX.) (X.)

resulting in the mobile and reversible formation of the conjugate acid (IX), followed by a step in which the ring opens to give an activated complex of the type (X), which is stabilised by resonance between structures derived from (X) by the electronic displacements indicated. Driving force for the reaction is provided by affinity of the lactol oxygen for a proton and by incipient formation of the aldimine structure, and might therefore be expected to increase with increasing basicity of the glycosidic nitrogen atom. Incipient formation of a hydrogen bond between the hydrogen attached to this atom and a solvent molecule may provide an additional driving force, which is here of secondary importance; this factor is absent from tertiary *N*-glycosides. In consequence these do not mutarotate by a base-catalysed mechanism such as is observed amongst the secondary *N*-glycosides, and in which the main driving force is provided by the affinity of a base molecule for a proton removable from the nitrogen atom, and incipient formation of an aldimine structure:



(XI.) (XII.)

The rate is determined by the group R through the second step which in this case results in formation of an activated complex (XII) in which the lactol oxygen carries a formal negative charge, stabilisation occurring to some extent by incipient interaction with a solvent molecule HB. Here, as in the acid catalysed mechanism, additional driving force may be supplied by the existence of strain in the lactol ring.

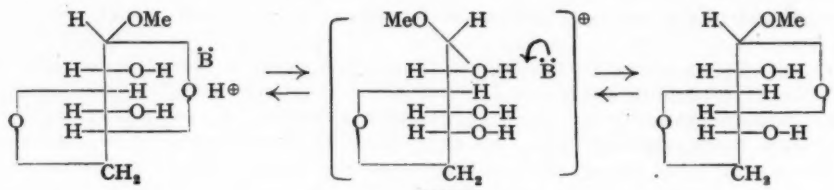
In interpreting the behaviour of the 6-amino-4-*d*-xylosidaminopyrimidines it is unnecessary to decide whether they are to be represented as secondary *N*-glycosides derived from 4 : 6-diaminopyrimidine, or whether they are in fact better formulated as secondary or tertiary *N*-glycosides derived from 6-amino-4-iminodihydropyrimidine (cf. Part III, *loc. cit.*), since in either case the argument remains qualitatively unaffected. That substances of the structures (I), (II), (V), and (VI) can exist as α- and β-forms showing little tendency to interconversion appears to be due to the circumstance that they are *N*-glycosides in which the nitrogen atoms concerned in the glycosidic linkage are very weakly basic. The introduction of the strongly basic amino-group into position 5 in the pyrimidine nucleus, *e.g.*, to give the structure (VII), may confidently be expected to produce a considerable increase in the electron availability at the glycosidic nitrogen atom; it seems probable that the increased driving force thereby available for the formation of the activated complex (X) is responsible for the promotion of αβ-isomerisation which accounts for the isolation of (VII) in only one form.

The second effect at work in the interconversion reactions of the 4-*d*-xylosidaminopyrimidine derivatives is one due to acetylation of the hydroxyl groups of the sugar residue. In Parts IX. (*loc. cit.*) and XIII it was pointed out that certain of these compounds show in quite a different connection behaviour which is most readily explained by assuming that chelation takes place between the glycosidic NH group and the carbonyl group of the acetyl residue located at C_2 in the sugar ring. The effect of such chelation would be to weaken the hold of the nitrogen atom on the hydrogen atom, thereby increasing electron availability at the former and facilitating configurational change at C_1. This effect appears to be responsible for the interconversion reaction which takes place when 5-nitroso-6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine-II (VI) is acetylated to give 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-I (VIII). If, as seems probable, it should prove that the two *o*-nitroxylidine-*l*-arabinosides of Kuhn and Ströbele (*loc. cit.*) are in fact αβ-isomers, their conversion into a common triacetyl derivative would receive a similar explanation. A further possible case of αβ-interconversion is provided by the acetylation of the isomeric 6-amino-4-*d*-xylosidaminopyrimidines and their 2-methylthio-derivatives. In each case the crystalline xyloside yields on acetylation very similar quantities of crystalline tetra-acetyl derivative to those obtained on similar treatment of the resinous xyloside mixture which has been shown (Parts IX and XI, *locc. cit.*) to consist largely of the isomeric xyloside. By analogy with the above mentioned nitroso-compounds it seems likely that the triacetyl derivatives of 6-amino-4-*d*-xylosidaminopyrimidine and its 2-methylthio-derivative show αβ-interconversion. This process would be hindered by acetylation at N_6, and it has been found that the isomeric 6-acetamido-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidines do not mutarotate in pyridine–acetic acid. In view of the behaviour of the triacetyl-5-nitroso-derivative (VIII) it may perhaps seem remarkable that the triacetyl-5-arylazo-derivative (III) should be capable of existence in α- and β-forms. A possible explanation is that the interconversion of these may be prevented by the hindering effect of the bulky 5-arylazo-substituent. When this group is removed reductively freedom of interconversion is not only restored in this way; it is further promoted by the increased electron availability due to the basic 5-amino-group, so that (IV) is isolated in only one form.

The furanose–pyranose interconversions described earlier in this paper for the aromatic amine *N*-glycosides obviously stand in a close relationship to the foregoing configurational changes, since both proceed *via* an activated complex in which the lactol ring is opened, and here again two phenomena, one involving considerations of velocity and the other those of equilibrium, are distinguishable. No satisfactory reasons can at present be given why aniline-*d*-riboside should be stable in alcohol at low temperatures as the pyranoside form, whereas at the boiling point the furanoside form appears to be the more stable, although parallel cases of the effects of temperature changes are well known : for example, Schlubach and Prochownick (*Ber.*, 1929, **62**, 1502) have shown that the amount of *d*-galactofuranose present in the equilibrium mixture in pyridine solution increases markedly with rise of temperature.

An interesting feature, however, emerges from our results with regard to the velocity phenomenon. Where change of lactol ring structure to a more stable form is possible on energetic grounds, it might be thought likely that every ring opening required to effect αβ-interconversion would also give rise to furanose–pyranose change. That this is not so is shown by the behaviour of aniline-α-*d*-ribofuranoside which in moist pyridine undergoes partial conversion into the β-form without any appreciable change in lactol ring structure; to promote conversion, addition of acetic acid is required. This point may be explained as follows. The main pathway of αβ-change in moist pyridine is most probably the base-catalysed mechanism, and the lactol oxygen atom in the activated complex (XII) carries a formal negative charge and would be expected to be more nucleophilic than that of an hydroxyl group on the adjacent carbon atom of the sugar ring; the linkage of the former oxygen to a hydrogen atom (from a solvent molecule HB) is only incipient, whereas in the latter it is complete. Closure in the lactol ring will therefore tend to involve this oxygen atom in preference to that of the adjacent hydroxyl group, and no change in lactol ring structure will take place. In the acid-catalysed mechanism which is possible in pyridine containing acetic acid the lactol oxygen atom is present in the transition state (X) as a formal hydroxyl group; the oxygen atom of an adjacent hydroxyl group will therefore

compete with it for closure with C_1 on an equal footing, and in time complete furanose ⟶ pyranose change will take place. In a complete analysis of the relative rates of αβ-isomerisation and of change in lactol ring structure it is possible that in other structures account might have to be taken of factors affecting the stability of the carbonium ion in the transition state, by analogy with the considerations which determine the extent of racemisation occurring during unimolecular solvolytic hydrolysis or alcoholysis of an optically active halide $CR_1R_2R_3Br$, but no such effect need be invoked in the present case. In this connection, however, reference may be made to the results of Haworth, Owen, and Smith (*loc. cit.*), who have shown that both α- and β-forms of 3 : 6-anhydro-methyl-*d*-glucopyranoside undergo acid-catalysed conversion into the corresponding furanosides with complete retention of configuration at C_1. This behaviour is the converse of that observed for aniline-α-*d*-ribofuranoside in moist pyridine, where configurational change takes place without alteration in the ring structure. Possibly the activated complex in the anhydro-compounds is stabilised by formation of a 3-membered oxide ring as in (XIII); formation of similar 3-rings seems to be responsible for related stereochemical effects, *e.g.*, in the addition of halogens to olefins and in the replacement of halogen by hydroxyl in α-halogenocarboxylate ions (for refs. see Wheland, " The Theory of Resonance," 1944, p. 242). Since both formation and rupture of such a ring would be accompanied by inversion at C_1, the over-all effect would be a retention of the original configuration.



(XIII.)

Experimental.

Triacetyl-d-*ribopyranosidoaniline.*—(a) *From* d-*ribopyranosidoaniline.* *d*-Ribopyranosidoaniline was prepared according to Lee, Solmssen, and Berger (U.S.P. 2,384,102) and had the following characteristics: m. p. 119°; $[\alpha]_D^{17°} = +60°$ ($c = 0{\cdot}95$ in dry pyridine), constant during 30 hours; $[\alpha]_D^{17°} = +60°$ (initial value) ⟶ $+48{\cdot}4°$ (final value, after 2 days) ($c = 0{\cdot}95$ in moist pyridine); $[\alpha]_D^{18°} = +71°$ (initial value) ⟶ $+43°$ (final value, after 4½ hours) ($c = 0{\cdot}75$ in pyridine containing 10% acetic acid). A portion (1·2 g.), acetylated as described by the above authors (*loc. cit.*), gave the triacetyl derivative as an amber resin (0·9 g.), $[\alpha]_D^{18°} = +29{\cdot}4°$ ($c = 3{\cdot}57$ in chloroform); no value is available from the above patent specification for comparison purposes. When the triacetyl compound (0·5 g.) was set aside for 3 days at 0° with saturated methanolic ammonia (10 c.c.) and the solvent removed at 20—25° under reduced pressure, the residue gave on crystallisation from alcohol *d*-ribopyranosidoaniline, m. p. 110°, $[\alpha]_D^{19°} = +60°$ ($c = 0{\cdot}93$ in dry pyridine).

(b) *From* d-*ribofuranosidoaniline.* The furanoside, prepared according to Lee and Berger (U.S.P. 2,384,104), had the following characteristics: m. p. 126—127°; $[\alpha]_D^{17°} = +180°$ ($c = 0{\cdot}85$ in dry pyridine), constant during 30 hours; $[\alpha]_D^{17°} = +180°$ (initial value) ⟶ $+161°$ (final value, after 3 days) ($c = 0{\cdot}85$ in moist pyridine); $[\alpha]_D^{18°} = +176°$ (initial value) ⟶ $+44°$ (final value, after 2½ hours) ($c = 1{\cdot}11$ in pyridine containing 10% acetic acid). A portion (0·8 g.) was acetylated as described by Lee and Berger (*loc. cit.*) giving triacetyl-*d*-ribopyranosidoaniline (0·8 g.) as an amber resin, $[\alpha]_D^{18°} = +32°$ ($c = 4{\cdot}58$ in chloroform). When this material (0·2 g.) was deacetylated as described in (a) above aniline-*d*-ribopyranoside (73 mg.) was obtained, m. p. 113°, $[\alpha]_D^{19°} = +61°$ ($c = 0{\cdot}66$ in dry pyridine).

Conversion of Triacetyl-d-*ribopyranosidoaniline into* 1 : 2 : 3 : 4-*Tetra-acetyl Ribose.*—The resinous triacetyl compound (1·4 g., obtained as described in (a) or (b) above) dissolved in alcohol (3·5 c.c.) was added to aqueous acetic acid (40 c.c. of 5%) and the mixture distilled in steam till no more aniline passed over. After decolorisation (charcoal) the remaining solution was evaporated to dryness under reduced pressure, and the residue dried by repeated evaporation with alcohol. It was dissolved in pyridine (5 c.c.), acetic anhydride (1 c.c.) added, and set aside overnight. Excess of acetic anhydride was then destroyed by addition of alcohol, solvents were removed under reduced pressure, and the residue was crystallised from alcohol. 1 : 2 : 3 : 4-Tetra-acetyl *d*-ribose separated in good yield, m. p. 110° undepressed in admixture with authentic material.

d-*Xylosidoaniline.*—(a) To *d*-xylose (5·76 g.) in water (8 c.c.) sufficient 3N-sulphuric acid was added to adjust the pH to 4·0 and a solution of aniline (4 c.c.) in alcohol (20 c.c.) was added. After 15 minutes at 25° the solution was concentrated in a vacuum desiccator over silica gel (2 days). The separated material (2·5 g.) had m. p. 142°, $[\alpha]_D^{19°} = -87°$ ($c = 2{\cdot}37$ in pyridine). Acetylation of this material (0·5 g.) by the usual method gave *triacetyl*-d-*xylosidoaniline*, m. p. 151°, $[\alpha]_D^{18°} = +25°$ ($c = 1{\cdot}82$ in chloroform) (Found: C, 58·1; H, 6·0; N, 4·0. $C_{17}H_{21}O_7N$ requires C, 58·1; H, 6·0; N, 4·2%).

(b) *d*-Xylose (5 g.) and aniline (3·75 c.c.) were heated under reflux in alcohol (50 c.c.) for 1½ hours, and the solution was concentrated to 30 c.c. under reduced pressure. The separated xyloside was collected, washed with alcohol, and recrystallised from the same solvent. Yield, 3·5 g., $[\alpha]_D^{19°} = -87°$ ($c = 2{\cdot}37$ in pyridine). Acetylation in the usual manner gave triacetyl-*d*-xylosidoaniline identical in properties with the material described under (a) above.

6-*Acetamido*-4-*triacetyl*-d-*xylosidaminopyrimidine.*—(a) 6-Amino-4-*d*-xylosidaminopyrimidine-I (0·4 g.; Part IX, *loc. cit.*) was shaken for 15 hours with pyridine (15 c.c.) containing acetic anhydride (5 c.c.) and a few drops of acetyl chloride, and then heated to 100° for ½ hour. After addition of alcohol, the solution was evaporated to dryness under reduced pressure and the residue extracted with boiling ethyl acetate (50 c.c.). On concentration of the extract to 5 c.c. the *tetra-acetyl* compound separated (0·13 g.). Recrystallised from alcohol it had m. p. 214—215° (Found in material dried at 110° in a vacuum over phosphoric oxide: C, 47·3; H, 5·7; N, 12·7. $C_{17}H_{22}O_8N_4,H_2O$ requires C, 47·7; H, 5·6; N, 13·1%).

(b) A portion (0·5 g.) of the resin contained in the mother-liquors from which 6-amino-4-*d*-xylosidaminopyrimidine-I separated was acetylated in the same manner, and gave a colourless crystalline solid (0·1 g.), m. p. 213—214° undepressed in admixture with the above tetra-acetyl compound.

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185. *Experiments on the Synthesis of Purine Nucleosides. Part XV. The Configuration of Some Synthetic Purine and Pyrimidine Glycosides.*

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The configuration at the glycosidic carbon atom in a number of synthetic purine and pyrimidine glycosides is deduced from a consideration of optical rotation data. The deductions, where comparable, accord with the results of the experimental determination of configuration described in Part XII (this vol., p. 833). It would appear that in all cases so far encountered where an α-glycoside is obtained by condensation of a sugar with a 4 : 6-diaminopyrimidine derivative, inversion of configuration occurs during the course of any subsequent purine glycoside synthesis so that the final product is always the stable β-glycoside.

An investigation of the oxidation of *N*-glycosides derived from primary amines (including 4-glycosidaminopyrimidines) with sodium metaperiodate and lead tetra-acetate is described. Neither of these reagents can be safely applied to the determination of lactol ring-structures in such compounds.

IT has been reported in earlier communications that xylosidisation of 4 : 6-diaminopyrimidine (Part IX; *J.*, 1944, 652) and 4 : 6-diamino-2-methylthiopyrimidine (Part XI; *J.*, 1945, 556) in hot alcoholic solution in presence of acid catalysts yields, in each case, a mixture of isomeric 4-*d*-xylosidaminopyrimidines. In the course of the synthesis of purine xylosides from these products it was observed that the isomerism disappeared on the introduction of an amino-group into position 5 of the pyrimidine nucleus so that each pair of isomers yielded finally only one 9-*d*-xylosidopurine. The 9-*d*-xylosidopurines so obtained have been shown to be pyranosides by the periodate oxidation method (Parts IX and XI, *locc. cit.*). The question naturally arose whether the difference between the isomeric pyrimidine xylosides mentioned above is due to α : β- or to furanose–pyranose isomerism. A definite answer to this question would be very desirable. It would affect the choice of possible methods for synthesising 9-glycofuranosidopurines, and it would be vital to an understanding of the interconversion of the isomers and would probably cast light on a number of interesting features of the behaviour of *N*-glycosides in general. We have sought to answer the question in several ways. An experimental determination of configuration at the glycosidic carbon atom in natural and synthetic purine glycosides has been reported in Part XII (*loc. cit.*) and an interpretation of the interconversion reactions as an aspect of mutarotation in *N*-glycosides has been given (Part XIV; preceding paper) which supports our original view that the pyrimidine xylosides are in fact α : β-isomers and have a pyranoside structure. The present paper records an independent approach to the configurational problem in pyrimidine and purine glycosides by examination of available optical rotation data, together with an account of some attempts to apply oxidation methods to the determination of lactol ring-structure in 4-glycosidaminopyrimidines.

According to modern theory (Kauzmann, Walter, and Eyring, *Chem. Rev.*, 1940, **26**, 339) optical activity results from light absorption in a chromophore being made anisotropic by the asymmetry of neighbouring groups. Chromophores showing absorption bands in the near ultra-violet (*e.g.*, carbonyl) are, on this view, particularly important in determining rotatory power, so that in glycosides containing pyrimidine or purine aglycones optical rotatory power should be closely connected with their ultra-violet absorption. This being so it would be expected that variation in the aglycone in such compounds would exert its main effect on rotatory power through change in ultra-violet absorption, rather than through change in asymmetrical environment of other chromophores, provided that variation of the aglycone did not involve substitution close to the sugar residue. A survey of the rotational data for the substituted aniline-*d*-glucosides given in Table I seems to support this view; of the glucosides showing mutarotation only those in which the direction of mutarotation is towards a more positive value have been included. The molecular optical rotations of these compounds, in which the ultra-violet absorption does not vary widely, are reasonably consistent, exceptions being found, as anticipated, mainly among the *o*-substituted anilineglucosides.

In the various pyrimidine and purine derivatives which have been synthesised, the absorption spectra of the aglycones are sufficiently similar to one another to warrant the view that the molecular rotations of the corresponding glycosides should be comparable in magnitude. That this is indeed so can be seen from Table II, wherein are listed data for the *d*-glucosides of theophylline, adenine, and hypoxanthine, in which the β-configuration may be assumed since they are all prepared from the silver salts of purines and α-acetobromoglucose. Comparison of adenine and theophylline compounds in this way is reasonable, since the aglycones differ in the pyrimidine and not in the iminazole portion of the molecule. Also in Table II the molecular rotation of theophylline-7-(β)-*d*-xylopyranoside, prepared from α-acetochloroxylose, is compared with the rotations of some 9-*d*-xylopyranosidoadenine derivatives, all of which evidently have the β-configuration. Further evidence of the same sort is provided by the molecular rotation values for the dialdehydes formed on periodate oxidation of the purine pentopyranosides in which asymmetry at all centres save the glycosidic carbon atom has been destroyed (Table II). These confirm the β-configuration assigned above to 9-*d*-xylopyranosidoadenine, and in addition indicate that the synthetic 9-*d*-ribopyranosidoadenine is also a

β-glycoside. The above deduction of an identical configuration in the 9-*d*-xylosidoadenine derivatives synthesised by our general synthetic method and in the products obtained using α-acetohalogenosugars is in agreement with the experimental findings recorded in Part XII (*loc. cit.*).

TABLE I.

Molecular Rotations of Substituted Aniline-d-glucosides

Aglycone.	$[M]_D$.	Solvent.	Ref.	Aglycone.	$[M]_D$.	Solvent.	Ref.
o-Toluidine	−26,800°	Methanol	1	*o*-Phenetidine	− 2,100°	Water	4
m-Toluidine	−27,700	,,	1	*p*-Anisidine	−23,300	Methanol	5
p-Toluidine	−26,200	,,	1	*o*-Anisidine	− 4,300	Water	6
vic.-o-Xylidine	−29,500	,,	1	*p*-Aminobenzoic acid	−33,500	Methanol	2
p-Xylidine	−29,000	,,	1	*p*-Chloroaniline	−11,600	,,	2
as.-o-Xylidine	−26,200	,,	1	*o*-Chloroaniline	−14,600	,,	2
as.-m-Xylidine	−28,600	,,	1	Ethyl *o*-aminobenzoate	+ 1,600	,,	2
s.-m-Xylidine	−29,000	,,	1	*o*-Nitroaniline	+ 7,800	Pyridine	7
α-Naphthylamine ...	−26,400	,,	2	5-Nitro-*o*-4-xylidine	+ 3,800	,,	7
β-Naphthylamine ...	−33,800	,,	3	*o*-Aminophenol	−23,800	Water	8
p-Phenetidine	−28,700	,,	3	*p*-Aminobenzenesulphonamide	−41,200	,,	8

[1] Hanaoka, *J. Biochem. Japan*, 1938, **28**, 109. [2] *Idem, ibid.*, 1940, **31**, 95. [3] Irvine and Gilmour, *J.*, 1910, **97**, 1552. [4] Amadori, *Atti R. Accad. Lincei*, 1931, **13**, 195. [5] *Idem., ibid.*, 1929, **9**, 226. [6] *Idem, ibid.*, 1931, **13**, 195. [7] Kuhn and Ströbele, *Ber.*, 1937, **70**, 777. [8] Kuhn and Birkofer, *ibid.*, 1938, **71**, 625

TABLE II.

		$[M]_D$.	Ref.
Purine Glucosides	Theophylline-7-(β)-*d*-glucopyranoside	− 800°	1
	Adenine-9-(β)-*d*-glucopyranoside	− 3,100	1
	Hypoxanthine-9-(β)-*d*-glucopyranoside	0	1
Purine Xylosides	Theophylline-7-(β)-*d*-xylopyranoside	−11,100	2
	Adenine-9-*d*-xylopyranoside	− 6,900	3
	2-Methyladenine-9-*d*-xylopyranoside	− 7,300	4
	2-Methylthioadenine-9-*d*-xylopyranoside	− 9,100	5
Dialdehydes from :	Theophylline-7-(α)-*d*-arabopyranoside	−14,900	2
	Theophylline-7-(β)-*d*-xylopyranoside	+14,700	2
	Adenine-9-*d*-xylopyranoside	+10,400 +11,400	3
	Adenine-9-*d*-ribopyranoside	+ 8,800	6

[1] Fischer and Helferich, *Ber.*, 1914, **47**, 210. [2] Lythgoe and Todd, *J.*, 1944, 592. [3] Kenner, Lythgoe, and Todd, *ibid.*, p. 652. [4] Baddiley, Lythgoe, and Todd, *ibid.*, p. 318. [5] Howard, Lythgoe, and Todd, *J.*, 1945, 556. [6] Baddiley, Kenner, Lythgoe, and Todd, *J.*, 1944, 657.

The assignment of configuration to the purine and pyrimidine glycosides can be approached in a slightly different way if Hudson's isorotation rules can be applied to such compounds. These rules are usually considered to depend on the validity of van't Hoff's principle of optical independence of asymmetric centres. Deviations from this principle are frequently encountered, and to explain them Kuhn and Freudenberg (*Ber.*, 1931, **64**, 703) introduced the concept of vicinal effects exerted by groups at some distance from an asymmetric centre. On the other hand, according to Gorin, Kauzmann, and Walter (*J. Chem. Physics*, 1939, **7**, 327), Hudson's rules rest on the symmetry of the sugar lactol ring and additivity in vicinal action of the groups attached to it. On either view introduction of a group showing strong ultra-violet absorption (*e.g.*, a pyrimidine or purine nucleus), and therefore probably exerting a strong vicinal effect, will disturb the situation. The magnitude of the vicinal effect of particular groupings is not easy to calculate, but for the purpose of this paper it is sufficient to examine available data in an empirical way. The aniline glycosides would offer a reasonable analogy for purine and pyrimidine glycosides, and Weygand (*Ber.*, 1940, **73**, 1278) has indeed already pointed out the strong vicinal effect of the anilino-residue in polyhydroxyalkylanilines. Unfortunately, the requisite reference compounds and data on α : β-isomers are not available in the aniline series, but substitutes can be found in the phenylglycosides where a very similar vicinal effect should be present. Table III presents the rotational data for several α : β-pairs of phenylglycosides, together with the A and B values calculated from them [$A = (M_\alpha - M_\beta)/2$ characteristic of the aglycone; $B = (M_\alpha + M_\beta)/2$ characteristic of sugar]; in the same table the corresponding values for the methylglycosides are given for comparison (all rotations are taken from Micheel, " Chemie der Zucker und Polysaccharide," Leipzig, 1938). The calculated A and B values for the phenylglycosides show the expected disturbance due to a vicinal effect, which had already been noted by Kuhn and Freudenberg (*loc. cit.*, p. 725). Nevertheless the relationship between the α : β-isomers is still evident, the α-glycosides having a more strongly positive rotation than the β-glycosides in the *d*-series. The A values (*ca.* 25,000—40,000°), which depend on the separation between their molecular rotations, remain fairly characteristic, and are distinctly higher than those calculated for the corresponding methyl compounds; the B values are also increased, but to a lesser degree. Constancy in A and B values cannot, of course, be expected on varying either sugar or aglycone. Mannosides and rhamnosides have been included in Table III because of scarcity of data and because the anomalies in applying isorotation rules to such compounds are not serious for the present purpose. The general conclusion to be drawn is that it is per-

missible to draw conclusions as to α : β-configuration from A and B values in compounds like the phenylglycosides, although strict conformity with isorotation rules cannot be expected.

Such information as is available regarding anilineglycosides appears to confirm these conclusions. Irvine and Gilmour (*J.*, 1909, **95**, 1545) have described two *p*-toluidineglucosides which mutarotate to the same equilibrium value and are almost certainly α : β-isomers. The molecular rotations of the isomers are in accord with the views above recorded (M_α, + 49,500°; M_β, − 26,200°; A, 37,850°, B, 11,650°). Another probable pair of α : β-isomers is to be found in the aniline-*l*-rhamnosides prepared respectively by Hermann (*J. Russ. Phys. Chem. Soc.*, 1905, **37**, 119; *Zentr.*, 1905, I, 1314) and Irvine and McNicoll (*J.*, 1910, 1455), although mutarotation evidence is lacking (M_α, − 12,000°; M_β, 32,800°; A, − 22,400°; B, 10,400°). The A values for these two pairs are in reasonably good agreement with those calculated for the corresponding phenylglycosides (Table III). The two aniline-*d*-glucosides of Irvine and Gilmour (*J.*, 1908, **93**, 1429) do not fit into the same scheme; it is noteworthy, however, that on mutarotation the " α " form is completely converted to the " β." In view of this and of the low A value for the pair (8000°) it seems likely that the one compound is a furanoside and the other a pyranoside (cf. Part XIV, preceding paper).

Accepting the argument advanced earlier as to the irrelevance of the variations in the aglycones and also the strictly limited applicability of the isorotation rules based on the data for the phenylglycosides in Table III, it is possible to draw up a list of the pyrimidine- and purine-xylosides and divide them into two groups, α and β. The molecular rotations are fairly consistent and reasonable A and B values can be calculated from the means (Table IV).

TABLE III.

	M_α.	M_β.	A.	B.
Phenylglycosides (in water or chloroform)				
d-Glucosides	46,200°	−18,200°	32,200°	14,000°
l-Rhamnosides	−25,400	21,000	−23,200	− 2,200
d-Mannosides	29,000	−18,300	23,650	5,300
Tetra-acetyl *d*-glucosides	70,000	−12,300	41,200	28,900
Tetra-acetyl *d*-mannosides	31,300	−26,600	29,000	2,400
Methylglycosides (in water or chloroform)				
d-Glucosides	30,800	− 6,600	18,700	12,100
l-Rhamnosides	−11,100	17,000	−14,100	3,000
d-Mannosides	15,200	−13,400	14,300	900
Tetra-acetyl *d*-glucosides	47,400	− 6,800	27,100	20,300
Tetra-acetyl *d*-mannosides	17,700	−18,100	17,900	− 200

TABLE IV.

		$[M]_D$.	Ref.
β-d-*Xylosides*	Adenine-9-*d*-xyloside	− 6,900	1
	2-Methyladenine-9-*d*-xyloside	− 7,300	2
	2-Methylthioadenine-9-*d*-xyloside	− 9,100	3
	6-*d*-Xylosidamino-2-methylpurine	− 9,000	2
	6-*d*-Xylosidamino-2-methylthiopurine	− 6,300	3
	6-Amino-4-*d*-xylosidamino-2-methylthiopyrimidine-I	− 5,800	3
	Mean	− 7,400	
α-d-*Xylosides*	6-Amino-4-*d*-xylosidaminopyrimidine-I	+37,300	1
	6-Amino-4-*d*-xylosidamino-2-methylpyrimidine	+40,400	2
	Mean	+38,850	

Hence, A = 23,200°; B = 15,800°. (For α- and β-methyl-*d*-xylopyranosides, A = 15,300°; B = 7000°.)

[1] Kenner, Lythgoe, and Todd, *J.*, 1944, 652. [2] Baddiley, Lythgoe, and Todd, *ibid.*, p. 318. [3] Howard, Lythgoe, and Todd, *J.*, 1945, 556.

If these arguments are valid it follows that in synthesising the xylosides of 2-methyladenine (Part VI, *J.*, 1944, 318) an inversion of configuration must have occurred, probably during hydrogenation of the intermediate azo-glycoside, although it escaped detection at the time. The conclusion that in the synthesis of the 2-methylthioadeninexylosides (Part XI; *loc. cit.*) the Series I intermediates have the same stable β-configuration as the final purines is in keeping with the fact that deacetylation of 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine (which is formed from either of the isomeric nitroso-xylosides) yields only 5-nitroso-6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine-I. It is also reasonable to conclude that in the condensation of 4 : 6-diaminopyrimidine with *d*-ribose, where only one glycoside was obtained (Part X, *J.*, 1944, 651), that glycoside ($[M]_D$ = − 8300°) is a β-*d*-riboside and it undergoes no inversion in the subsequent stages of the synthesis of 9-β-*d*-ribopyranosidoadenine ($[M]_D$ = − 10,100°).

The simplicity and accuracy of the periodate oxidation method for the determination of lactol ring-structure and configuration of purine glycosides (Part VIII, *J.*, 1944, 592; Part XII, *loc. cit.*) made a study of the applicability of this method, or of some modification, to the 4-glycosidaminopyrimidines attractive. Various observations recorded in the literature suggested that the method might not apply to glycosides containing an NH group; for example, Karrer and Mayer (*Helv. Chim. Acta*, 1937, **20**, 407) found that periodate causes

complete breakdown of ethyl *N*-carbethoxyglucosaminate, and a similar observation was made by Neuberger (*J.*, 1941, 47) in the case of ethyl *N*-benzoylglucosaminate. On the other hand, it has been reported by Nicolet and Shinn (*J. Amer. Chem. Soc.*, 1939, **61**, 1615) that *N*-acetylserine is only very slowly attacked by periodic acid, and Niemann and Hays (*ibid.*, 1940, **62**, 2960) showed that *N*-acetyl-*d*-glucosylamine behaves normally with the same reagent. The oxidation of a number of NH-glycosides was therefore examine titrimetrically. The results listed in Table V show that, in general, complete oxidation of the glycosides occurred, pentosides consuming *ca.* 4 and hexosides *ca.* 5 mols. of oxidant per mol. of glycoside. The values obtained were moderately consistent but the unexplained excessive uptakes of *o*-nitroaniline-*d*-xyloside and 6-acetamido-4-*d*-xylosidamino-2-methylpyrimidine-I would tend to destroy any confidence in the method applied to an unknown compound. It is, of course, evident that the method in any case, although it might distinguish a hexoside from a pentoside, could give no information as to lactol ring-structure or configuration. Furanosides and pyranosides presumably give the same products and all asymmetric centres are destroyed in the oxidation which in all probability follows the course shown in the scheme below.

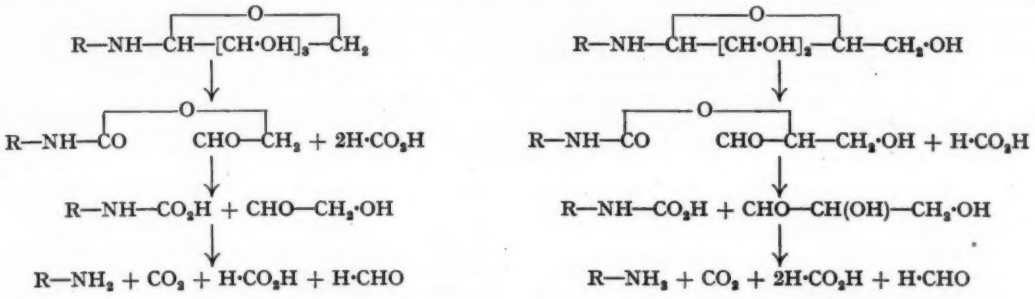

TABLE V.

Compound.	Mols. of oxidant per mol. (approx.). Sodium metaperiodate.	Lead tetra-acetate.
o-Nitroaniline-*d*-xyloside	4—5	3
o-Nitroaniline-*l*-arabinoside	4	4—5
p-Carboxyaniline-α-*d*-ribopyranoside	—	3
o-Nitroaniline-*d*-glucoside	5	4
p-Toluidine-*d*-glucoside	5	5—6
6-Acetamido-4-*d*-xylosidamino-2-methylthiopyrimidine-I	5—6	3·5
4-Amino-6-acetamido-2-methylthiopyrimidine	1	0·5

Oxidation of the same series of glycosides with lead tetra-acetate was next examined. The results, also indicated in Table V, are, like those obtained using periodate, unsatisfactory, although it is of interest to note that in a number of cases the oxidation stops, or at any rate becomes very slow, after the first stage in the scheme set out above. If this were general, lead tetra-acetate might be used to differentiate between furanosides and pyranosides. Unfortunately the extent of oxidation appears to depend on the nature of the aglycone, so that *p*-toluidineglucoside shows an unduly large uptake, while aniline-*d*-ribopyranoside undergoes such rapid and extensive oxidation to deep red products that the reaction cannot be followed quantitatively. The general conclusion to be drawn from these experiments is that neither periodate nor lead tetra-acetate can be employed satisfactorily to determine lactol ring-structure of glycosides of unknown structure containing a free NH group attached to the glycosidic carbon atom. In certain cases some information might be obtained using lead tetra-acetate (*e.g.*, it would seem from Table V that 6-acetamido-4-*d*-xylosidamino-2-methylthiopyrimidine-I is almost certainly a pyranoside), but little confidence could be reposed in the method when applied to unknown compounds.

EXPERIMENTAL.

Oxidations with Sodium Metaperiodate.—A weighed quantity (100—200 mg.) of glycoside was suspended in sodium metaperiodate solution (20 c.c. of *ca.* 0·25M) in a graduated flask, and the mixture left at room temperature. After *ca.* 20 hours the contents of the flask were diluted to 50 c.c. and unchanged metaperiodate estimated iodimetrically on an aliquot; further estimations were made at suitable intervals until a constant value was reached.

o-*Nitroaniline*-l-*arabinoside* (Kuhn and Strõbele, *loc. cit.*). Uptake of oxidant (mols./mol.): 21 hours, 4·14; 96 hours, 4·2; 168 hours, 4·2.

o-*Nitroaniline*-d-*glucoside*. Uptake of oxidant (mols./mol.): 22 hours, 4·88; 48 hours, 4·95; 96 hours, 4·99.

o-*Nitroaniline*-d-*xyloside* (Kuhn and Strõbele, *loc. cit.*). Uptake of oxidant (mols./mol.): 24 hours, 3·66; 48 hours, 4·16; 172 hours, 4·52; 168 hours, 4·75.

p-*Toluidine*-d-*glucoside* (Kuhn and Dansi, *Ber.*, 1936, **67**, 1749). Uptake of oxidant (mols./mol.): 18 hours, 5·02; 47 hours, 5·14.

6-*Acetamido*-4-d-*xylosidamino*-2-*methylthiopyrimidine-I* (Baddiley, Lythgoe, and Todd, *J.*, 1944, 318). Uptake of oxidant (mols./mol.): 72 hours, 5·18; 144 hours, 5·56.

In the course of oxidations of *o*-nitroanilineglycosides, methylenebis-*o*-nitroaniline was always precipitated, doubtless as a result of interaction of formaldehyde and *o*-nitroaniline produced by complete oxidation of the sugar residues; in the same way, *p*-toluidineglucoside gave on oxidation with periodate 1 : 3 : 5-tri-*p*-tolyl-1 : 3 : 5-hexahydrotriazine.

Oxidations with Lead Tetra-acetate.—The substance to be oxidised (50—100 mg.) was suspended in a solution of lead

tetra-acetate (50 c.c. of 0·0588M) in pure acetic acid, and the mixture maintained at 23° in a thermostat. Aliquots (2 c.c.) were removed from time to time and unchanged lead tetra-acetate estimated iodimetrically.

o-*Nitroaniline*-l-*arabinoside*. Uptake of oxidant (mols./mol.): 1 hour, 0·99; 3 hours, 1·89; 9·5 hours, 3·06; 34 hours, 4·03; 48 hours, 4·36; 53 hours, 4·45; 71 hours, 4·50.

o-*Nitroaniline*-d-*glucoside*. Uptake of oxidant (mols./mol.): 3 hours, 0·45; 10 hours, 1·79; 23 hours, 2·45; 34 hours, 2·91; 49 hours, 3·36; 97 hours, 4·02; 120 hours, 4·14; 168 hours, 4·4.

o-*Nitroaniline*-d-*xyloside*. Uptake of oxidant (mols./mol.): 3 hours, 1·75; 23 hours, 2·63; 46 hours, 2·95; 54 hours, 3·05; 71 hours, 3·30.

p-*Toluidine*-d-*glucoside*. Uptake of oxidant (mols./mol.): 5 hours, 4·96; 25 hours, 5·83; 101 hours, 6·42. In other experiments the uptake ranged between 5 and 6 mols./mol.

6-*Acetamido*-4-d-*xylosidamino*-2-*methylthiopyrimidine*-*I*. Uptake of oxidant (mols./mol.): 3 hours, 0·22; 22 hours, 2·20; 48 hours, 3·22; 71 hours, 3·74; 120 hours, 4·10; 168 hours, 4·50.

p-*Carboxyaniline*-d-*ribopyranoside* (Lee, Solmssen, and Berger, U.S.P. 2,384,102). Uptake of oxidant (mols./mol.): 3 hours, 2·38; 23 hours, 2·9; 45 hours, 3·14; 49 hours, 3·16; 53 hours, 3·25.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for grants.

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186. *Some* p-*Alkoxybenzenesulphonamides and their* N-*Chloro-derivatives.*

By W. E. HANBY and H. N. RYDON.

Eight p-*alkoxybenzenesulphonamides* ($RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2$; R = n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, n-$C_{10}H_{21}$, n-$C_{12}H_{25}$, and n-$C_{16}H_{33}$) have been prepared and converted into the corresponding *sodio*-p-*alkoxybenzenesulphonchloroamides*, $RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NNaCl$.

IN connection with another investigation it was necessary to prepare a series of derivatives of chloramine-B, $Ph{\cdot}SO_2{\cdot}NNaCl$, containing aliphatic side-chains of varying length. Of the possible ways in which such side-chains might have been introduced into the chloramine-B molecule the simplest, from the preparative standpoint, appeared to be in the form of *p*-alkoxy-groups; we have accordingly prepared eight *p*-alkoxy-derivatives of chloramine-B containing alkyl groups with from four to sixteen carbon atoms in the chain.

The *sulphonyl chlorides* of the appropriate phenyl alkyl ethers were converted into the *sulphonamides* best by treatment with aqueous ammonia, since the action of ammonium carbonate (Huntress and Carten, *J. Amer. Chem. Soc.*, 1940, **62**, 511) when applied by us to p-n-*hexadecyloxybenzenesulphonyl chloride* gave, not the desired amide, but *bis*-(p-n-*hexadecyloxybenzenesulphon*)*imide*, $(C_{16}H_{33}O{\cdot}C_6H_4{\cdot}SO_2)_2NH$.

The compounds p-$RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2$ (R = n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, or n-$C_{10}H_{21}$) were converted directly into the required *sodio*-p-n-*alkoxybenzenesulphonchloroamides*, p-$RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NNaCl$, by treatment with alkaline sodium hypochlorite; owing to unfavourable solubility relationships this method failed with p-$RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2$ (R = n-$C_{12}H_{25}$ or n-$C_{16}H_{33}$); these were, therefore, first converted into the p-n-*alkoxybenzenesulphondichloroamides*, p-$RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NCl_2$, which gave the required *sodio-monochloroamides* on warming with sodium hydroxide solution. All these *p*-alkoxy-derivatives of chloramine-B were effective chlorinating agents and, as expected, the solubility in water decreased and the solubility in non-polar solvents increased with increasing chain length of the alkyl group.

EXPERIMENTAL.

The phenyl alkyl ethers used in this work were prepared, in excellent yield, from highly purified specimens of the alkyl bromides (for generous supplies of which we are much indebted to Dr. G. S. Hartley) by reaction with sodium phenoxide in alcoholic solution, essentially as described by Hartley (*J.*, 1939, 1828).

Preparation of p-n-*Alkoxybenzenesulphonamides*.—The appropriate phenyl alkyl ether (1 mol.) was treated gradually with concentrated sulphuric acid (125 c.c. usually sufficed) until the product was completely soluble in hot water (cf. Hartley, *loc. cit.*). The reaction mixture was then warmed with carbon tetrachloride and the lower layer of sulphuric acid run off; addition of light petroleum (b. p. 40—60°) to the carbon tetrachloride layer precipitated the sulphonic acid as an oil which was dissolved in alcohol and neutralised with alcoholic potash. The precipitated potassium salt was filtered off, dried at 100°, and then treated with phosphorus pentachloride (1·5 mols.); after the initial vigorous reaction had subsided the mixture was warmed on the water-bath for a short time and then poured on crushed ice. The precipitated sulphonyl chloride was collected, treated with an excess of warm ammonia solution (*d* 0·880) with hand stirring, and then kept at room temperature overnight. The precipitated sulphonamide was collected and crystallised from aqueous alcohol.

The following were prepared in this way (the quoted yields are based on the phenyl alkyl ether):

p-n-Butyloxybenzenesulphonamide (40% yield), needles, m. p. 108° (Huntress and Carten, *loc. cit.*, give m. p. 103—104°) (Found: C, 52·4; H, 6·5; N, 6·3. Calc. for $C_{10}H_{15}O_3NS$: C, 52·4; H, 6·5; N, 6·1%).

p-n-*Amyloxybenzenesulphonamide* (53% yield), needles, m. p. 96° (Found: C, 54·2; H, 6·7; N, 5·8. $C_{11}H_{17}O_3NS$ requires C, 54·3; H, 7·0; N, 5·8%).

p-n-*Hexyloxybenzenesulphonamide*, short needles, m. p. 100° (Found: C, 56·1; H, 7·7; N, 5·45. $C_{12}H_{19}O_3NS$ requires C, 56·0; H, 7·4; N, 5·4%); *sodium* salt, m. p. 265—270° (decomp.), pearly leaflets from water (Found: C, 51·8; H, 6·9; N, 5·0; Na, 8·2. $C_{12}H_{18}O_3NSNa$ requires C, 51·6; H, 6·45; N, 5·0; Na, 8·2%).

p-n-*Heptyloxybenzenesulphonamide* (65% yield), needles, m. p. 99° (Found: C, 57·6; H, 7·6; N, 5·25. $C_{13}H_{21}O_3NS$ requires C, 57·6; H, 7·7; N, 5·2%).

p-n-*Octyloxybenzenesulphonamide* (65% yield), leaflets, m. p. 104° (Found: C, 58·9; H, 8·3; N, 4·9. $C_{14}H_{23}O_3NS$ requires C, 58·9; H, 8·1; N, 4·9%).

p-n-*Decyloxybenzenesulphonamide* (61% yield), flattened needles, m. p. 107° (Found: C, 61·6; H, 8·8; N, 4·6. $C_{16}H_{27}O_3NS$ requires C, 61·4; H, 8·6; N, 4·4%).

p-n-*Dodecyloxybenzenesulphonyl chloride*, m. p. 37°, needles from light petroleum (b. p. 40—60°) (Found: C, 60·2; H, 8·05; Cl, 9·6. $C_{18}H_{29}O_3ClS$ requires C, 59·9; H, 8·0; Cl, 9·85%). p-n-*Dodecyloxybenzenesulphonamide*, short flattened needles, m. p. 109° (Found: C, 63·4; H, 9·3; N, 4·3. $C_{18}H_{31}O_3NS$ requires C, 63·3; H, 9·1; N, 4·1%).

p-n-*Hexadecyloxybenzenesulphonyl chloride* (95% yield), m. p. 58° (Found: C, 63·5; H, 9·0. $C_{22}H_{37}O_3ClS$ requires C, 63·4; H, 8·9%). p-n-*Hexadecyloxybenzenesulphonamide* (88% yield), m. p. 111° (Found: C, 66·5; H, 9·6; N, 3·55. $C_{22}H_{39}O_3NS$ requires C, 66·5; H, 9·8; N, 3·5%); *sodium* salt, m. p. 310° (decomp.) (Found: C, 63·4; H, 9·2; N, 3·4. $C_{22}H_{38}O_3NSNa$ requires C, 63·0; H, 9·1; N, 3·3%). In another experiment the sulphonyl chloride (265 g.), dissolved in chloroform (30 c.c.), was treated with ammonium carbonate (10 g.) and the mixture evaporated to dryness. The product was ground with water, filtered, and again washed with water and this crude product (23 g.) was crystallised from acetic acid yielding *bis*-(p-n-*hexadecyloxybenzenesulphon*)*imide*, m. p. 89—92° (Found: N, 1·7. $C_{44}H_{75}O_6NS_2$ requires N, 1·8%); this imide (16 g.) was converted, in 85% yield, into the amide, m. p. mixed m. p. 111°, by warming with aqueous ammonia (*d* 0·880; 35 c.c.) and methanol (170 c.c.).

Chlorination of p-*Alkoxybenzenesulphonamides.*—(i) *Lower members.* With the six lowest members of the series the following procedure was used. The sulphonamide (50 g.) was dissolved in 10% sodium hydroxide solution (150 c.c.), warming if necessary. 2N-Sodium hypochlorite (200 c.c.) was then added with stirring; after cooling in ice the product was filtered off, washed with a little water, and crystallised from water.

The Table gives details for the various *sodio*-p-n-*alkoxybenzenesulphonchloroamides* prepared in this way.

Compounds $RO{\cdot}C_6H_4{\cdot}SO_2{\cdot}NNaCl$.

R.	Yield, %.	Cryst. form.	M. p.*	Analysis.
n-Butyl	69	Needles	162°	Found: N, 4·8; Cl, 11·2; available Cl, 22·4. $C_{10}H_{13}O_3NClSNa,2H_2O$ requires N, 4·35; Cl, 11·0; available Cl, 22·1%.
n-Amyl	71	Leaflets	158	Found: N, 4·5; available Cl, 22·4. $C_{11}H_{15}O_3NClSNa,H_2O$ requires N, 4·4; available Cl, 22·3%.
n-Hexyl	96	Needles	160	Found: N, 4·4; available Cl, 21·6. $C_{12}H_{17}O_3NClSNa,H_2O$ requires N, 4·2; available Cl, 21·4%.
n-Heptyl	63	Needles	156	Found: N, 4·3; available Cl, 21·4. $C_{13}H_{19}O_3NClSNa$ requires N, 4·3; available Cl, 21·7%.
n-Octyl	88	Needles	162	Found: N, 4·6; available Cl, 20·6. $C_{14}H_{21}O_3NClSNa$ requires N, 4·1; available Cl, 20·8%.
n-Decyl	71	—	152	Found: C, 49·3; H, 7·1; N, 3·6; available Cl, 18·3. $C_{16}H_{25}O_3NClSNa,H_2O$ requires C, 49·5; H, 7·0; N, 3·6; available Cl, 18·3%.

* All with decomposition.

(ii) *Higher members.* The following procedure was used for the dodecyl and hexadecyl compounds. The finely powdered sulphonamide was treated with excess of filtered bleach paste and excess of glacial acetic acid was added gradually with stirring. After an hour the solid product was collected and re-treated with filtered bleach paste and acetic acid. The product from this second chlorination, the sulphondichloroamide, was crystallised from purified light petroleum (b. p. 40—60°). This product was converted into the sodium sulphonchloroamide by warming (50—70°) for 15 minutes with 10% sodium hydroxide solution (5 c.c./g.); the resulting paste was cooled and filtered, and the sodium salt recrystallised from purified dioxan. The overall yield was about 80%.

The following were prepared in this way:

p-n-*Dodecyloxybenzenesulphondichloroamide*, clusters of needles, m. p. 47° (Found: C, 52·3; H, 7·1; N, 3·3; Cl, 17·6; available Cl, 34·6. $C_{18}H_{29}O_3NCl_2S$ requires C, 52·7; H, 7·1; N, 3·4; Cl, 17·3; available Cl, 34·6%). *Sodio*-p-n-*dodecyloxybenzenesulphonchloroamide*, m. p. 145° (decomp. at 195—200°) (Found: available Cl, 17·8. $C_{18}H_{29}O_3NClSNa$ requires available Cl, 17·9%).

p-n-*Hexadecyloxybenzenesulphondichloroamide*, needles, m. p. 63—64° (Found: C, 56·35; H, 8·2; N, 3·0; available Cl, 29·2. $C_{22}H_{37}O_3NCl_2S$ requires C, 56·65; H, 8·0; N, 3·0; available Cl, 30·4%). *Sodio*-p-n-*hexadecyloxybenzenesulphonchloroamide*, m. p. 215° (decomp.) (Found: N, 2·9; Cl, 7·85; available Cl, 15·5. $C_{22}H_{37}O_3NClSNa$ requires N, 3·1; Cl, 7·8; available Cl, 15·6%).

We are indebted to the Chief Scientific Officer, Ministry of Supply, for permission to publish these results and to Mr. J. E. Cave-Browne-Cave for technical assistance. The micro-analyses were carried out by Mr. G. Ingram.

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187. *Studies in the Polyene Series. Part XXIV. The C_{17} Acid and C_{18} Ketone related to Vitamin A.*

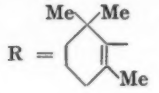
By SIR IAN HEILBRON, E. R. H. JONES, and D. G. O'SULLIVAN.

The recent publication by Arens and van Dorp (*Nature*, 1946, **157**, 190) of a description of the synthesis of "vitamin A acid" *via* the C_{17} acid and C_{18} ketone necessitates the publication of work done in our laboratory along similar lines. The crystalline C_{17} acid (II; R′ = H) is obtained in 15% yield from β-ionone by a Reformatsky reaction with γ-bromocrotonic ester and it is converted, through the acid chloride, into the C_{18} ketone (IV). Attempts to effect Reformatsky reactions with ω-bromosorbic ester and β-ionone and other ketones have been abortive.

THE use of γ-halogenocrotonic esters in Reformatsky reactions was first studied by Fuson, Arnold, and Cooke (*J. Amer. Chem. Soc.*, 1938, **60**, 2272), who obtained rather poor yields of unsaturated esters in condensations of the bromo- and iodo-compounds with benzaldehyde and *cyclo*hexanone. As was noted by these authors, the usefulness of this reaction is limited by the availability of the γ-halogenocrotonates. In 1942 Ziegler *et al.* (*Annalen*, **551**, 80) described the convenient preparation of methyl γ-bromocrotonate by bromination of

methyl crotonate with *N*-bromosuccinimide, and in a simultaneous paper (*ibid.*, p. 120) details of Reformatsky reactions with the bromo-ester and benzaldehyde, cinnamaldehyde, etc., were published. Cook and Schoental (*J.*, 1945, 288) have successfully condensed methyl bromocrotonate with ketotetrahydrophenanthrene, noting the many possible applications of this method in the synthesis of hydroaromatic fused-ring systems.

In the earliest synthetic work in the vitamin A field, β-ionone was condensed with ethyl bromoacetate and zinc to give, after dehydration at 170°, ethyl β-ionylideneacetate (I, R′ = Et) (Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878). This reaction is by no means as straightforward as would appear from the original description (cf. Young, Andrews, and Cristol, *J. Amer. Chem. Soc.*, 1944, **66**, 520; Sobotka, Bloch, and Glick, *ibid.*, 1943, **65**, 1961; Young, Andrews, and Lindenbaum, *ibid.*, 1944, **66**, 2131; Sobotka,



(I.) R·CH:CH·CMe:CH·CO_2R′ R·CH:CH·CMe:CH·CH:CH·CO_2R′ (II.)

(III.) R·CH:CH·CMe:CH·CH:CH·CH:CH·CO_2H R·CH:CH·CMe:CH·CH:CH·COMe (IV.)

Darby, Glick, and Bloch, *ibid.*, 1945, **67**, 403). Our own investigations carried out over a period of several years provide additional evidence of its complexity and will be reported in due course.

In view of the difficulties encountered with ethyl β-ionylideneacetate, only pure β-ionone (regenerated from its semicarbazone by the method devised by Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727) was employed in Reformatsky reactions with methyl γ-bromocrotonate. Condensation proceeded normally in benzene solution and, according to spectrographic and other evidence, the crude product contained a considerable portion of the dehydrated ester (II; R′ = Me), which after distillation exhibited a broad absorption band with a maximum in the region of 3100 A. (ε = 12,500). The gummy acid obtained on hydrolysis with cold alcoholic potassium hydroxide readily crystallised in contact with ether, giving the C_{17} acid (II; R′ = H), m. p. 160°, in an overall yield of 15% from β-ionone. The structure assigned to this acid is supported by ozonolysis evidence, a 34% yield of geronic acid (isolated as semicarbazone) being obtained, and also by a quantitative hydrogenation, 3·9 moles of hydrogen being absorbed. The light-absorption properties of the acid ($\lambda_{max.}$ 3250 A., ε = 32,500) and of the pure *methyl* ester ($\lambda_{max.}$ 3230 A., ε = 33,000), prepared with diazomethane, are in accord with the structure given, being displaced towards longer wave-lengths by the expected amount when compared with the data for pure β-ionylideneacetic acid (I; R′ = H) (maxima, 2910, 2810, and 2590 A.; ε = 13,000, 13,000, and 12,000, respectively).

The success obtained in condensing the γ-bromocrotonate with β-ionone appeared to augur well for the extension of this type of reaction to sorbic esters, in the expectation of obtaining the C_{19} acid (III), and later, by using a methylsorbic ester, the acid corresponding to vitamin A itself. *Methyl ω-bromosorbate* was made in 65% yield by reaction between methyl sorbate and *N*-bromosuccinimide. It showed the expected light-absorption properties, and its structure was proved by the isolation of bromoacetaldehyde and the methyl ester of the half aldehyde of fumaric acid (as 2 : 4-dinitrophenylhydrazones) on ozonolysis. Numerous attempts to condense this ester, not only with β-ionone, but also with acetophenone and *cyclo*hexanone, under a great variety of conditions (use of benzene, toluene, xylene, and anisole as solvents, in the presence of activated zinc and magnesium, etc.) were entirely abortive since, although the metal usually went into solution, comparatively small amounts of high-boiling non-ketonic products were obtained from any of these experiments. [Note added in proof. Karrer and Schwyzer (*Helv. Chim. Acta*, 1946, **29**, 1191) have described the preparation of methyl ω-bromosorbate and they also report unsuccessful attempts to condense it with ketones.]

Attention was then redirected to the C_{17} acid (II; R′ = H), and the possibility of converting it to the C_{18} ketone (IV) was examined. Although on addition of the crude methyl ester to methylmagnesium iodide a crystalline complex separated rapidly, no ketonic material with the correct light-absorption properties was isolated on treatment of the product with the Girard reagent. Conversion of the acid into its chloride, followed by treatment with dimethylcadmium according to Gilman and Nelson (*Rec. Trav. chim.*, 1936, **56**, 518), was an obvious alternative, but in the case of β-ionylideneacetic acid, anomalous results have been reported (Young, Andrews, and Cristol, *loc. cit.*) when this procedure was used. It is by no means certain, however, that the method employed by Young *et al.* for the preparation of the acid chloride is free from objection. Consequently, the C_{17} acid was treated with thionyl chloride in the presence of pyridine, giving a 50% yield of the *chloride*, which not only possessed the anticipated light-absorption properties, but also furnished the crystalline C_{17} acid on hydrolysis. A preliminary condensation with dimethylcadmium yielded a ketonic product, the light-absorption properties of which were consistent with the presence of a considerable proporton of the required C_{18} ketone.

At this stage in our investigations Arens and van Dorp (*loc. cit.*) briefly reported the synthesis of " vitamin A acid " *via* the C_{17} acid mentioned above and the corresponding C_{18} ketone, the latter having been obtained by the action of methyl-lithium on the acid (cf. Gilman and van Ess, *J. Amer. Chem. Soc.*, 1933, **55**, 1258). As a result of this anticipation of our own work it seemed desirable to publish a detailed description * of our results as soon as the preparation of the C_{18} ketone by the dimethylcadmium method had been completed. Reaction with the acid chloride by this means gives a ketonic product (separated by Girard reagent P), from which the semicarbazone of the C_{18} ketone, with m. p. 191° (Arens and van Dorp, *loc. cit.*, give 189°, corr.), was isolated, the light-absorption data (maximum, 3420 A., ε = 64,500) being in agreement with those quoted

* A preliminary account was published in *Nature* (1946, **157**, 485).

by the Dutch workers. Treatment of the semicarbazone with 3N-sulphuric acid in the presence of boiling petroleum (b. p. 80—100°) gave the C_{18} ketone (IV) which exhibited maximal light absorption in the expected region (maximum, 3350 A., $\varepsilon = 38{,}000$). [Note added in proof. A full account of the work of Arens and van Dorp has now appeared (*Rec. Trav. chim.*, **1946**, **65**, 338). We have adduced additional evidence of the structure of " vitamin A acid " by an ozonolysis experiment which gave geronic acid in 15% yield.]

Our studies on this C_{18} ketone are being continued in attempts to convert it into vitamin A itself or other biologically active derivatives. Work has been in progress for some time on condensations of the acyclic C_{14} and C_{15} aldehydes and the C_{17} and C_{18} ketones (Batty, Burawoy, Heilbron, Jones, and Lowe, *J.*, **1937**, 755; Barraclough, Batty, Heilbron, and Jones, *J.*, **1939**, 1549) with γ-bromocrotonate and bromoacetate, respectively, in the expectation of obtaining acids of the lycopene type which, if Karrer and Bretscher's contention (*Helv. Chim. Acta*, **1943**, **26**, 1758) be correct (cf. Gillam, Heilbron, Jones, and Lederer, *Biochem. J.*, **1938**, **32**, 405), will be related to vitamin A_2.

Experimental.

(Light-absorption data determined in alcohol.)

Condensation of β-Ionone with Methyl γ-Bromocrotonate.—The C_{17} *Acid* [1-(2′ : 6′ : 6′-*Trimethyl*-Δ¹′-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*triene*-6-*carboxylic Acid*] (II; R′ = H).—A solution of pure β-ionone (39 g.; regenerated from the semicarbazone, m. p. 146°; Heilbron, Johnson, Jones, and Spinks, *loc. cit.*) and methyl γ-bromocrotonate (36 g.; $n_D^{12°}$ 1·5022) in benzene (50 c.c.) was added in nitrogen during 1 hour to a stirred mixture of boiling benzene (350 c.c.) and zinc needles (13 g.) together with a crystal of iodine. After being stirred and refluxed for 6 hours, the cooled mixture was stirred with 5% acetic acid, and the benzene layer was separated off, washed with bicarbonate solution and water, and dried. The benzene was removed under reduced pressure in nitrogen, and distillation of the residue gave (i) β-ionone (23·5 g.) and (ii) crude methyl ester (20 g.), b. p. 120—130°/10^{-2} mm., as a pale yellow viscous oil. Two fractionations of (ii) gave material with b. p. 55° (bath temp.)/10^{-3} mm., $n_D^{19°}$ 1·5632. Light absorption: Broad maximum, 2900—3240 A., $\varepsilon = 12{,}500$.

The crude ester (5 g.) was hydrolysed for 24 hours in a solution of potassium hydroxide (3 g.) in methanol (25 c.c.) in nitrogen. Acidification with phosphoric acid (20%) and isolation with ether gave a gummy acid product (3·8 g.), which partly solidified on trituration with cold ether. Crystallisation from acetone yielded the pure C_{17} acid (1·4 g.) as pale yellow plates, m. p. 160° (Found: C, 78·1; H, 9·15. Calc. for $C_{17}H_{24}O_2$: C, 78·4; H, 9·3%). On shaking with Adams's catalyst, a solution of the acid (0·26 g.) in alcohol (3 c.c.) absorbed 93·8 c.c. of hydrogen at 20° and 760 mm., equivalent to $\equiv$ 3·9.

Methyl Ester.—A solution of the pure acid (2·6 g.) in ether (20 c.c.), cooled in ice-salt, was treated dropwise with diazomethane (0·4 g.) in ether. After 2 hours at −5°, the ether was removed, and distillation of the residue gave the *methyl* ester (1·4 g.) as a pale yellow liquid, b. p. 65° (bath temp.)/10^{-3} mm., $n_D^{20°}$ 1·5630 (Found: C, 78·8; H, 9·4. $C_{19}H_{26}O_2$ requires C, 78·8; H, 9·55%).

Ozonolysis of the C_{17} *Acid.*—A solution of the acid (1 g.) in carbon tetrachloride (30 c.c.) was treated with a slow stream of ozonised oxygen for 24 hours. " AnalaR " acetic acid (15 c.c.) was then added to dissolve the precipitated ozonide, and the solution was ozonised for a further 24 hours. Water (200 c.c.) was added, and the mixture was heated under reflux for 1 hour and then evaporated to a syrupy consistency under diminished pressure. More water (100 c.c.) was added, and the procedure repeated. The acidic portion of the product, isolated in the usual manner, was extracted with boiling water (5 c.c.), and the filtered extract was treated with a solution of semicarbazide hydrochloride (0·6 g.) and sodium acetate (1·1 g.) in water (3 c.c.). After standing at 0° for some hours, the crude semicarbazone was filtered off and crystallised from ethyl acetate, giving pale yellow crystals (0·4 g.), m. p. 157—160°. Recrystallisation from the same solvent gave geronic acid semicarbazone (0·31 g.; 34%), m. p. 163°, undepressed on admixture with an authentic specimen, m. p. 163°.

C_{17} *Acid Chloride* [1-(2′ : 6′ : 6′-*Trimethyl*-Δ¹′-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*triene*-6-*carboxyl Chloride*].—The crystalline acid (13 g.) in dry ether (130 c.c.) was cooled to −5° in nitrogen and pure pyridine (7·9 g.) was gradually added. This was followed by the dropwise addition of pure thionyl chloride (5·9 g.) at such a rate that the temperature of the reaction mixture could be maintained at −5° to 0°. The mixture was then stirred at 0° for 2 hours, and finally warmed in a bath at 50° for 1 hour. After cooling in ice, dry hydrogen chloride was introduced into the stirred mixture until it became acidic, and the precipitate of pyridine hydrochloride was filtered off. Evaporation of the filtrate and distillation of the residue gave the *acid chloride* (6·7 g.), b. p. 55° (bath temp.)/10^{-3} mm., $n_D^{20°}$ 1·5660 (Found: Cl, 12·5. $C_{17}H_{23}OCl$ requires Cl, 12·7%). Light absorption: Maximum, 3230 A., $\varepsilon = 29{,}000$.

Hydrolysis of the acid chloride with ice cold methyl-alcoholic potassium hydroxide gave an acidic product from which the crystalline C_{17} acid was recovered in 50% yield.

C_{18} *Ketone* [1-(2′ : 6′ : 6′-*Trimethyl*-Δ¹′-cyclo*hexenyl*)-3-*methylhexa*-1 : 3 : 5-*trien*-7-*one*] (IV).—A slight excess of methyl bromide in dry ether was added to magnesium (0·96 g.) in nitrogen, anhydrous cadmium chloride (3·68 g.) was then added to the resulting methylmagnesium bromide, and the mixture was stirred rapidly for 30 minutes. After addition of the acid chloride (6·7 g.) in ether at 20° during 30 minutes and refluxing on the steam-bath for 3 hours, the cooled mixture was poured on a stirred mixture of ice and ammonium chloride. The product isolated by means of ether was refluxed in nitrogen for 1 hour with Girard reagent P (5 g.) and acetic acid (5 c.c.) in alcohol (50 c.c.), and the crude ketonic material (2·8 g., 45%), isolated in the usual manner, was converted into the semicarbazone with a slight excess of semicarbazide acetate in methyl-alcoholic solution. After crystallisation of the derivative from ethyl acetate–methanol (1 : 1), the C_{18} ketone semicarbazone (1·6 g.) was obtained as pale yellow plates, m. p. 191° (Found: C, 72·1; H, 9·3. Calc. for $C_{19}H_{29}ON_3$: C, 72·3; H, 9·25%).

The semicarbazone (1·5 g.) was refluxed in nitrogen for 20 hours with 3N-sulphuric acid (10 c.c.) and petroleum (10 c.c.; b. p. 80—100°). This gave the C_{18} ketone (0·8 g.) as a pale yellow viscous oil, b. p. 85° (bath temp.)/10^{-4} mm., $n_D^{16°}$ 1·5670 (Found: C, 83·3; H, 10·1. Calc. for $C_{18}H_{26}O$: C, 83·7; H, 10·15%).

Methyl ω-Bromosorbate.—A mixture of powdered *N*-bromosuccinimide (178 g.) and methyl sorbate (504 g.; m. p. 11°, b. p. 90°/35 mm., $n_D^{22°}$ 1·5025, $\lambda_{max.}$ 2580 A., $\varepsilon = 31{,}500$) was stirred and heated at 120° until the bulk of the bromoimide had dissolved. After a further 15 minutes at this temperature the mixture was cooled, and the separated succinimide was filtered off and washed with carbon tetrachloride. The filtrate was washed with sodium carbonate solution and water, and then dried and evaporated, and distillation gave methyl sorbate (360 g.) and *methyl ω-bromosorbate* (133 g.), b. p. 75°/1 mm., $n_D^{20°}$ 1·5456 (Found: C, 41·2; H, 4·45; Br, 38·7. $C_7H_9O_2Br$ requires C, 41·0; H, 4·4; Br, 39·0%). Light absorption: Maximum, 2650 A.; $\varepsilon = 19{,}000$.

Ozonolysis of Methyl ω-Bromosorbate.—Ozonised oxygen was passed through a solution of the ester (2 g.) in acetic acid (15 c.c.) for 24 hours, after which zinc dust (1 g.) and water (100 c.c.) were added and the mixture was refluxed for

1 hour. On subsequent distillation, ten fractions, each of about 4 c.c., were collected and these were treated with 2 : 4-dinitrophenylhydrazine sulphate. The derivatives obtained from the later fractions were readily purified by crystallisation from 80% methanol, giving orange-yellow needles (1·4 g.; 50% yield), m. p. 195° (Found : N, 18·9. Calc. for $C_{11}H_{10}O_6N_4$: N, 19·0%). For the 2 : 4-dinitrophenylhydrazone of the aldehyde corresponding to the monomethyl ester of fumaric acid, Heinänen (*Chem. Abs.*, 1938, **32**, 7893) gives m. p. 194°.

The derivatives obtained from the earlier fractions were extracted with hot methanol, and crystallisation of the insoluble material from alcohol–ethyl acetate (1 : 1) gave 0·87 g. (29% yield) of the 2 : 4-*dinitrophenylhydrazone* of bromoacetaldehyde, as orange-coloured needles, m. p. 150°, undepressed on admixture with a specimen prepared from bromoacetal (Found : N, 18·4; Br, 26·2. $C_8H_7O_4N_4Br$ requires N, 18·5; Br, 26·4%).

Note added in Proof. Ozonolysis of "Vitamin A acid."—A solution of the acid (100 mg.) in carbon tetrachloride (4 c.c.) was treated as described above for the C_{17} acid. The crude semicarbazone (20 mg.) had m. p. 153—156° and after crystallisation from ethyl acetate gave geronic acid semicarbazone (11 mg.; 15%), m. p. 163°, undepressed on admixture with an authentic specimen.

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188. *Nitration in Sulphuric Acid. Part I. The Nature of the Nitrating Agent in Nitric–Sulphuric Acid Mixtures.*

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A wide range of physical and chemical evidence is reviewed including some new experiments described in the two following papers (Parts II and III) and it is shown that nitric acid is present in mixed acids mainly in the form of the cation NO_2^+ produced according to the equation $HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-$. The nitronium ion NO_2^+ is identified as the active species upon which the vigorous nitrating action of mixed acid depends.

According to Graebe ("Geschichte der organischen Chemie," Berlin, 1920, p. 142), a mixture of nitric and sulphuric acids was first used for nitration in the aromatic nucleus 100 years ago, when Muspratt and Hofmann converted nitrobenzene into dinitrobenzene with the mixed acids (*Mem. Proc. Chem. Soc.*, 1846, **3**, 111; *Annalen*, 1846, **57**, 201). Although this mixture has since come into universal use, particularly as a very powerful reagent for relatively difficult nitrations, the function of the sulphuric acid has not yet been fully explained. The idea that sulphuric acid "absorbs" the water formed during nitration, and so facilitates nitration by a mass-action effect, is excluded by the work of Spindler (*Ber.*, 1883, **16**, 1253), which proved that the retarding influence of water in the nitration of benzene was not due to any chemical action of water on nitrobenzene. Aromatic nitration is not reversible. A more hopeful hypothesis is that sulphuric acid converts nitric acid into an "active form," which is the actual nitrating agent; and the view to be developed in this paper is that the nitrating agent present in mixed acids is the NO_2^+ cation, formed when nitric acid is dissolved in sulphuric acid according to the equation $NO_2{\cdot}OH + 2H_2SO_4 \rightleftharpoons NO_2^+ + OH_3^+ + 2HSO_4^-$ (cf. Westheimer and Kharasch, *J. Amer. Chem. Soc.*, in the press). This equilibrium is analogous to that proved to be established (Hantzsch, *Z. physikal. Chem.*, 1909, **65**, 41; Hantzsch and Berger, *Z. anorg. Chem.*, 1930, **190**, 321; Angus and Leckie, *Proc. Roy. Soc., A*, 1935, **149**, 327; **150**, 615; *Trans. Faraday Soc.*, 1935, **31**, 958; Klinkenberg, *Rec. Trav. chim.*, 1937, **56**, 749; *Chem. Weekblad*, 1938, **35**, 197) when nitrous acid is dissolved in sulphuric acid, namely, $NO{\cdot}OH + 2H_2SO_4 \rightleftharpoons NO^+ + OH_3^+ + 2HSO_4^-$.

It may be pointed out that according to this view the water necessarily eliminated in a nitration is in fact released reversibly, but before the actual nitration (itself irreversible) takes place.

The physical and chemical properties of mixtures of nitric acid, sulphuric acid, and water have been studied by numerous workers. Consideration of results from all sources has led to general recognition that the molecular complexion of such mixtures depends primarily upon the molecular proportions of water and sulphuric acid present; for these components interact almost quantitatively to form the ionised hydrate, $[OH_3]^+[HSO_4]^-$, regardless of the nitric acid, whose fate is decided by whether water or molecular sulphuric acid remains thereafter in excess. In an equimolecular mixture of water and sulphuric acid, nitric acid is present mainly in the form $NO_2{\cdot}OH$. An excess of water converts the nitric acid into nitrate ion, but an excess of sulphuric acid produces a new "third form," the nature of which is discussed below.

The properties of a dilute solution of nitric acid in sulphuric acid monohydrate and absolute sulphuric acid are summarised and compared in Table I.

In the following discussion it will be necessary to review some of this evidence in detail and it will be shown : (1) that when dissolved in an excess of sulphuric acid, nitric acid is present in an altered form; (2) that it is in fact present as a cation; (3) that this cation is NO_2^+ (the nitronium ion); (4) that the cation NO_2^+ is the active nitrating agent of mixed acids.

1. *Qualitative Evidence that a New Species is present in Mixed Acids.*—a. *Ultra-violet absorption.* The conclusion that a new species derived from nitric acid is present in a mixture of nitric and sulphuric acids was argued by Hantzsch (*Ber.*, 1925, **58**, 941; *Z. physikal. Chem.*, 1930, **149**, 161; v. Halban and Eisenbrand, *ibid.*, 1928, **132**, 433) from the fact that the absorption spectra of ultra-violet light due to the nitrate ion and to the undissociated nitric acid molecule were absent, or much diminished, in solutions of nitric acid in con-

TABLE I.

Property.	Solution of nitric acid in : Sulphuric acid monohydrate (84·5% w/w).	Absolute sulphuric acid (100% w/w).	References.
Partial pressure of nitric acid	Maximum	Zero	See Section 1, b and appendix.
Ultra-violet absorption	Resembles that of absolute HNO_3	Solution is unusually transparent	See Section 1, a.
Cryoscopic *i* factor	1	4	See Sections 1, d and 3, a.
Effect upon conductivity of medium	Small	Large	See Section 2, a.
Raman frequencies	Those due to $HO{\cdot}NO_2$, and 1400 cm.$^{-1}$ (weak)	None due to $HO{\cdot}NO_2$; 1400 cm.$^{-1}$ (intense)	See Sections 1, c, 3, b, 3, e.

centrated sulphuric acid. In sulphuric acid, therefore, nitric acid must be present in some other form which is transparent in this region of the spectrum.

b. *Vapour pressures of nitric acid over mixed acids.* Vapour-pressure measurements are considered in detail in an appendix to this paper (p. 874). An immediate argument is that the conversion of nitric acid into a less volatile form in concentrated sulphuric acid and in oleum is evident from the fact that these solvents retain dissolved nitric acid at high temperatures. We have found that solutions of 0·00124 mole of nitric acid in 15 ml. each of weak oleum, 98% sulphuric acid, and 85% sulphuric acid, heated to 200° for 5 minutes, lose respectively 1, 10, and 92% of the nitric acid by vaporisation.

c. *Raman spectra.* The Raman spectra of mixtures of nitric acid, sulphuric acid, and water have been studied very comprehensively by Chédin (*Ann. Chim.*, 1937, **8**, 243). The outstanding feature is a Raman shift $\Delta\nu = 1400$ cm.$^{-1}$, which can be detected in 100% nitric acid but is stronger in mixed acids having a molar ratio $H_2SO_4/H_2O > 1$, its intensity increasing with diminishing water or increasing oleum content. This frequency is not due to the nitric acid molecule or to the nitrate ion (or to the normal nitrogen pentoxide molecule) and must represent some new species derived from nitric acid.

d. *Cryoscopy.* Cryoscopic results show that nitric acid dissolves in sulphuric acid with production of several particles per molecule added (see Section 3, a, where references are given).

2. *Evidence for a Cationic Form of Nitric Acid.*—The formation of a nitric acid cation in sulphuric acid solution was proved by the outstanding discoveries of Hantzsch, but additional evidence is now available. The position may be summarised as follows.

a. *Conductivity.* Solutions of nitric acid in absolute sulphuric acid have a high electrical conductivity (*e.g.*, Saposchnikov, *Z. physikal. Chem.*, 1904, **49**, 697; 1905, **51**, 609; **53**, 225; Hantzsch, refs. in para. 3, a; Bergius, *Z. physikal. Chem.*, 1910, **72**, 338; Ussanowitsch, *Acta Physicochim. U.R.S.S.*, 1935, **2**, 239). Ions must therefore be produced, yet the evidence of the absorption spectrum shows clearly that the NO_3^- ion is not present, and Hantzsch took the view that the nitric acid is converted into nitracidium ions according to equations (3) and (4) (see below).

b. *Isolation of salts.* A clear proof that nitric acid can exist as a cation is furnished by the isolation (Hantzsch, 1925, *loc. cit.*; Hantzsch and Berger, *Ber.*, 1928, **61**, 1328) of two crystalline salts formed by direct combination of nitric and perchloric acids. Their compositions appeared from analysis to be $[H_2NO_3]^+[ClO_4]^-$ and $[H_3NO_3]^{++}[ClO_4]_3^-$; and they were found, by conductivity measurements, to be binary and ternary electrolytes, respectively, in nitromethane solution. When these solutions were electrolysed, nitric acid accumulated at the *cathode*.

c. *Migration to the cathode in electrolysis.* Direct evidence of the presence of a nitric acid cation in sulphuric acid solution by experiments on its migration during electrolysis has hitherto been lacking. We have now found conditions for obtaining this essential demonstration. Experiments on the simultaneous cathode migration of nitric acid and the barium ion in oleum solution show that nitric acid migrates from anode to cathode and that the nitric acid cation has a mobility of 2—4 times that of the barium ion. Migration of nitric acid dissolved in 98·7% sulphuric acid has also been demonstrated, but less conclusively. Details and additional experiments are given in Part II (following paper).

3. *Evidence for the* NO_2^+ *Ion.*—Although the Hantzsch cations, $H_2NO_3^+$ and $H_3NO_3^{++}$, may exist in concentrated nitric acid, in nitric–perchloric acid mixtures (para. 2, b), and perhaps in mixed acids containing a relatively high proportion of water, it seems probable that in oleum media and in mixed acids containing little water the NO_2^+ ion is the prevailing form. In order to test this suggestion, it is necessary to reinterpret many of the recorded data and to provide detailed proof of the validity of the equation we propose.

The following five equations represent the various views which have been advocated :

	No. of particles formed from 1 mol. of HNO_3 in excess H_2SO_4.	
(1) $2HNO_3 + H_2SO_4 \longrightarrow N_2O_5 + H_3O^+ + HSO_4^-$	$\frac{1}{2}$	(Saposchnikov)
(2) $HNO_3 + 2H_2SO_4 \longrightarrow NO_2{\cdot}O{\cdot}SO_2{\cdot}OH + H_3O^+ + HSO_4^-$	3	(Markovnikov)
(3) $HNO_3 + H_2SO_4 \longrightarrow H_2NO_3^+ + HSO_4^-$	2	(Hantzsch)
(4) $HNO_3 + 2H_2SO_4 \longrightarrow H_3NO_3^{++} + 2HSO_4^-$	3	(Hantzsch)
(5) $HNO_3 + 2H_2SO_4 \longrightarrow NO_2^+ + 2HSO_4^- + H_3O^+$	4	(This paper, and Westheimer and Kharasch, *loc. cit.*)

It will be seen that Markovnikov's suggestion is identical with our view provided that it is recognised that the mixed anhydride is in fact ionised in sulphuric acid solution.

The idea, represented by equation (1), that nitrogen pentoxide is present in mixed acids was rejected by Hantzsch (*loc. cit.*, 1925) but has nevertheless been advocated by several authors in recent years. A critical examination of the evidence on which this view was based is recorded in the appendix to this paper, but it may be pointed out that, bearing in mind the volatility of nitrogen pentoxide (which is greater than that of nitric acid), the fact that mixtures of nitric acid with concentrated sulphuric acid yield anhydrous 100% nitric acid and not nitrogen pentoxide on distillation, is in itself conclusive.

Evidence giving direct support to equation (5) will now be considered.

a. *Cryoscopic data.* Cryoscopic measurements in sulphuric acid have been made by Hantzsch (*Z. physikal. Chem.*, 1907, **61**, 257; **62**, 178, 626; 1908, **65**, 41; 1909, **68**, 204), by Oddo and Scandola (*ibid.*, 1908, **62**, 243), by Robles and Moles (*Anal. Fís. Quím.*, 1934, **32**, 474), by Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1933, **55**, 1900), and by Treffers and Hammett (*ibid.*, 1937, **59**, 1708). Hantzsch supposed that nitric acid acts as a base towards the stronger sulphuric acid, according to equations (3) and (4). These equations require that nitric acid dissolved in sulphuric acid should yield 2 and 3 particles per molecule of nitric acid respectively; *i.e.*, the van't Hoff factor i should be 2 or 3. On the other hand, our equation (5) requires $i = 4$.

Hantzsch himself deduced $i = 3$, but the most satisfactory of his results for nitric acid were obtained by adding potassium nitrate to a slightly aqueous sulphuric acid; and, allowing for the potassium hydrogen sulphate formed, these gave i factors of 3·80, 3·80, and 3·84 for nitric acid. Robles and Moles reported values of 3·26, 2·60, and 2·46; but their observations are subject to a considerable error, pointed out by Hammett, in that absolute 100% sulphuric acid was used as solvent. Correct results are obtained by working with sulphuric acid to which just enough water has been added to repress self-ionisation to a minimum: otherwise the observed depressions may be as low as one-half of the true value.

This question has been carefully re-examined by Hughes and Ingold, who have kindly given us permission to quote their results, as yet unpublished. The measurements were made by following Hammett's procedure. In sulphuric acid (with 0·2 mole % of water), nitric acid gave i factors of 3·82 (mean of five additions) and 3·80 (mean of five more), in close agreement with Hantzsch's value and confirming the formation of NO_2^+.

b. *Raman spectra of mixed acids and related systems.* The Raman spectra of some mixed acids and of possible components are compared in Table II, compiled chiefly from data of Chédin (*loc. cit.*; *Mem. Services chim. de l'État*, 1944, **31**, 113; cf. Médard, *Compt. rend.*, 1934, **199**, 1615). Chédin adopted Saposchnikov's view that nitrogen pentoxide is formed in mixed acids. However, the spectrum of this system is quite different from that of nitrogen pentoxide in inert solvents, and from the infra-red spectrum of gaseous nitrogen pentoxide; Chédin concluded that mixed acid contains nitrogen pentoxide in a "different chemical form," which he first supposed to be a polymer of nitrogen pentoxide, later the association complex N_2O_5,H_2SO_4. Nitrogen pentoxide dissolved in nitric acid he supposed to exist in a similar (polymerised or solvated) condition, to which in either medium the frequencies $\Delta\nu$ 1050 and 1400 cm.$^{-1}$ were allotted.

TABLE II.

Raman Spectrum of Mixed Acid and Related Systems.

System examined.	Frequencies observed, cm.$^{-1}$.	Notes.
Nitrate ion	1050	
Bisulphate ion	1044	
N_2O_5 in $CHCl_3$ or CCl_4	860 (weak), 1244, 1335 (strong)	Infra-red absorption at 880 and 1315 cm.$^{-1}$
" $POCl_3$	1249, 1337 (strong)	
N_2O_5 in nitric acid (<20% w/w N_2O_5)	Lines of $HO{\cdot}NO_2$ molecules + 1050 and 1400	
N_2O_5 in oleum	Lines of oleum medium + 1082 and 1400	Strong, 1400 sharp
Absolute nitric acid	Lines of $HO{\cdot}NO_2$ molecules + 1050, 1120, and 1400	Sharp, but very weak
Anhydrous mixture:		
1. 0·20 HNO_3 + 0·80 H_2SO_4	1050 and 1400 + lines of $HO{\cdot}NO_2$ + lines of H_2SO_4	Intense, 1400 sharp. Very weak
2. 0·15 HNO_3 + 0·85 H_2SO_4	1050 and 1400 + lines of H_2SO_4	Intense, 1400 sharp. Lines of $HO{\cdot}NO_2$ absent
0·046 HNO_3–0·482 H_2O–0·472 H_2SO_4	Lines of H_2SO_4,H_2O + lines of $HO{\cdot}NO_2$ + 1400	Relatively strong; 1400 line very weak

A much simplified interpretation of the Raman spectrum of concentrated mixed acids proceeds from the assumption that ions of the mixed anhydride, $[NO_2]^+[HSO_4]^-$, are present. Before pursuing this in detail we shall point out strong grounds for attributing the 1400 cm.$^{-1}$ frequency to the NO_2^+ ion.

An ion NO_2^+ would be iso-electronic with the molecule CO_2, differing from it only in the nuclear charge of the central atom, which would be + 7 instead of + 6. It would be expected to adopt the same linear configuration as carbon dioxide, since it is known that four-covalent nitrogen has the same stereochemical disposition of its valencies as carbon; and having the same symmetrical arrangement of two oxygen atoms about a central atom, it should resemble carbon dioxide closely in its modes of vibration. The relationship is somewhat similar to that between NO^+ and N_2, pointed out by Angus and Leckie (*loc. cit.*).

The sole fundamental vibrational frequency of the carbon dioxide molecule revealed in its Raman spectrum is of about 1320 cm.$^{-1}$, represented in the Raman spectrum by two lines of comparable intensity, owing to resonance between this frequency and the overtone of another. If NO_2^+ and CO_2 vibrate similarly, only the breathing vibration of NO_2^+ will likewise be active in the Raman spectrum and, since this ion has one extra unit charge on the central nucleus as compared with the carbon dioxide molecule, it is to be expected that the frequency of this vibration will be somewhat higher than that for carbon dioxide. These considerations are consistent with the observed value $\Delta\nu = 1400$ cm.$^{-1}$; moreover, the degree of depolarisation (Chédin, *loc. cit.*, found 0·188—0·20) confirms that the line must arise from a totally symmetrical vibration, as this view requires. [Compare the pair of frequencies at 1286 and 1388 cm.$^{-1}$ in the Raman spectrum of carbon dioxide which have a degree of depolarisation of 0·18 and 0·14, respectively (Langseth and Nielsen, *Physical Rev.*, 1934, **46**, 1057).]

In the mixed acid, the strong frequency of the bisulphate ion is of 1044 cm.$^{-1}$, and the coexistence of this pair of lines in anhydrous mixed acid is thus natural. The spectrum of molecular nitric acid is undetected in anhydrous mixtures of nitric and sulphuric acids unless the proportion of the former exceeds about 18 moles %, in harmony with the observation that the partial pressure of nitric acid at 0° is zero up to a similar composition (Vandoni, *Mem. Services chim. de l'État*, 1944, **31**, 87). The intensity of the 1400 cm.$^{-1}$ line, and hence the concentration of nitronium ion, diminishes on adding water to the anhydrous acid mixture, and the line vanishes when the mole fraction of water slightly exceeds that of sulphuric acid.

Weak lines at 1050 and 1400 cm.$^{-1}$ are observed in the spectrum of absolute nitric acid. By a coincidence, the frequency of the bisulphate ion is nearly identical with that of the nitrate ion, which is of 1050 cm.$^{-1}$; absolute nitric acid evidently contains a proportion of nitronium and nitrate ions. The 1400 line is very weak and corresponds to a low concentration of nitronium ion, which, therefore, may accompany the ion $H_2NO_3^+$ (and possibly $H_3NO_3^{++}$) proposed by Hantzsch (1925, *loc. cit.*) in the absolute acid. Addition of nitrogen pentoxide to nitric acid reinforces the pair of lines at 1050 and 1400 cm^{-1}, and it was largely on this ground that the frequencies were allotted originally to nitrogen pentoxide (Susz and Briner, *Helv. Chim. Acta*, 1935, **18**, 378). There is ample evidence, however, from the vapour pressure, electrical conductivity, and rate of decomposition of this system (Berl and Saenger, *Monatsh.*, 1929, **54**, 1042; Eyring and Daniels, *J. Amer. Chem. Soc.*, 1930, **52**, 1472, 1486) that the components react with the production of an ionised compound (or compounds) which exists in equilibrium with at most only a few units % of molecular nitrogen pentoxide. With little doubt the lines observed are of nitronium and nitrate ions, which are in direct or indirect equilibrium with nitrogen pentoxide.

c. *Kinetics of nitration.* The general validity of equation (5), and in particular the presence of the bisulphate ions on the right-hand side of this equation, are supported by the fact that its use has enabled us to give a quantitative interpretation of the speeds of nitration, under a wide range of conditions, of 2 : 4-dinitrotoluene and other substances, a full account of which will be given in subsequent papers.

d. *The influence of nitric acid upon the oleum–water titration.* The " free " sulphur trioxide of oleum may be titrated quantitatively with water (yielding sulphuric acid) until the liquid ceases to fume (Brand, this vol., p. 585). The first step in the reaction between nitric and sulphuric acids may be written $HO{\cdot}NO_2 + H_2SO_4 = NO_2^+ + HSO_4^- + H_2O$; this suggests that the titration of a solution of nitric acid in oleum should require less water than is needed to titrate the pure oleum. This effect is observed, and is treated in more detail in Part III. Numerically we find that each mole of nitric acid reduces the water titration of oleum by 1·5 moles of water. Moreover, experiment shows that the addition of an inorganic bisulphate to oleum also lowers a subsequent water-titration, but by 0·5 mole of water for each mole of bisulphate (regardless of the nature of the cation). The total effect of nitric acid can be interpreted by using the equation of this paragraph (cf. equation 5); it is made up of a lowering of water-titration of 0·5 mole due to the bisulphate ion, and of 1·0 mole due to the water eliminated between the two acids. The experimental result is incompatible with equations (1)—(4).

e. *The nature of the cognate reaction between nitric acid and pyrosulphuric acid.* Evidence on this point is once again provided by Chédin's data. Addition of nitrogen pentoxide to fuming sulphuric acid leads to the appearance of the 1400 cm.$^{-1}$ frequency together with a line observed between 1076 and 1094 cm.$^{-1}$. Chemically, it seems likely that nitrogen pentoxide and pyrosulphuric acid will interact to form the ionised mixed anhydride, and therefore that the nitronium ion is formed by reaction thus: $N_2O_5 + H_2S_2O_7 = NO_2^+ + HS_2O_7^- + HONO_2$, $HONO_2 + 2H_2S_2O_7 = NO_2^+ + HS_2O_7^- + 2H_2SO_4$. The frequency of approximately 1085 cm.$^{-1}$ is now therefore allocated, by analogy, to the anion, $HS_2O_7^-$, which accompanies the nitronium ion in oleum solution.

The spectrum of a solution of nitric acid in oleum resembles in principle that of the solution in absolute sulphuric acid, and possesses two characteristic features: (i) The sole frequency of " nitric acid " in dilute solution is of 1400 cm.$^{-1}$; the fraction of nitric acid which must be added before the lines of molecular nitric acid appear, increases with the strength of the oleum. (ii) Progressive addition of nitric acid to oleum weakens the lines of pyrosulphuric acid and strengthens those of sulphuric acid.

The latter observation, which shows that water is eliminated in the reaction between nitric and pyrosulphuric acids, can be used to estimate the number of moles of water liberated per mole of nitric acid dissolved. Consider, for example, the mixtures I and II of 10% and 20% (w/w) of nitric acid, respectively, in an oleum of 60% (w/w; 65 mol. %) " free " sulphur trioxide examined by Chédin (*loc. cit.*). The spectrum of

the oleum medium possesses frequencies due to pyrosulphuric acid and sulphur trioxide only; these are given also by mixture I (together with the 1400 cm.$^{-1}$ line), but in mixture II they are much diminished in intensity and are now accompanied by the lines of sulphuric acid. The gross molar composition of these mixtures is as follows in mole fractions:

	HNO_3.	SO_3.	H_2SO_4.
I	0·132	0·562	0·306
II	0·256	0·482	0·262

We shall examine the following different views of the process of mixing: (1) that no water is liberated (Hantzsch, 1925, *loc. cit.*), $HNO_3 + H_2S_2O_7 = H_2NO_3^+ + HS_2O_7^-$; (2) that 0·5 mole of water is liberated per mole of nitric acid, yielding nitrogen pentoxide; (3) that one mole of water is set free per mole of nitric acid, $HNO_3 + H_2S_2O_7 = NO_2^+ + HS_2O_7^- + H_2O$ (cf. equation 5). The detection of molecular sulphuric acid is incompatible with (1), which cannot account for its formation. Also, (2) is unsatisfactory: the 0·256 mole of nitric acid in II would yield 0·128 mole of water, which would convert 0·256 mole of sulphur trioxide into pyrosulphuric acid. The remaining sulphur trioxide (0·226 mole) would unite with sulphuric acid, of which therefore only 0·036 mole would be free. This amount is quite insufficient to account for the observed strength of the sulphuric acid lines.

On the other hand, (3) requires 0·256 mole of water to be liberated, which would convert 0·482 mole of sulphur trioxide into 0·226 mole of pyrosulphuric acid and 0·030 mole of sulphuric acid. The total quantity of the latter would be therefore 0·292 mole, and in fact this is evident in the Raman spectrum. For mixture I, however, the liberated water would be only 0·132 mole, which would form pyrosulphuric acid with 0·264 mole of sulphur trioxide: the remaining sulphur trioxide (0·298 mole) would leave only 0·008 mole of free sulphuric acid, insufficient to be detected. At the same time, the fact that the Raman spectrum of sulphuric acid is not detected in this mixture excludes the possibility that more than one mole of water is formed per mole of nitric acid. This and similar calculations, which can be made from Chédin's results, provide further clear evidence in favour of the view we advocate.

4. NO_2^+ *as the Nitrating Agent in Mixed Acids.*—A mixture of nitric acid with sulphuric acid (or oleum) is among the most active nitrating agents known. Benford and Ingold (*J.*, 1938, 929) place sulphuric acid in a class by itself as a "fast" nitration solvent. It is clear that the NO_2·OH molecule is not the efficient nitrating agent present in mixed acids: first, because nitric acid is a less effective nitrating agent when alone than when it is mixed with sulphuric acid; and secondly, because, in mixtures of nitric acid, sulphuric acid, and water, molecular nitric acid, NO_2·OH, is in maximum concentration when the molar ratio $H_2O/H_2SO_4 \sim 1$, whereas mixed acids with so high a proportion of water to sulphuric acid have lower or zero nitrating power * (the actual speed of nitration varying, of course, with the nature of the substance nitrated). It has been suggested that the actual nitrating agent in mixed acids is a dehydration product of nitric acid; and Markovnikov's idea (*Ber.*, 1899, **32**, 1441) that the mixed anhydride NO_2·O·SO_2·OH is the nitrating agent seems particularly plausible. Nitrogen pentoxide has also been proposed (for a recent example, cf., *e.g.*, Titov, *J. Gen. Chem. Russ.*, 1941, **11**, 1125) and, in fact, Klemenc and Schöller (*Z. anorg. Chem.*, 1924, **141**, 231) found identical velocities for nitration of *m*-xylene-4:6-disulphonic acid, in anhydrous sulphuric acid, by nitric acid and by nitrogen pentoxide, N_2O_5 being counted as $2HNO_3$. But the nitrogen pentoxide molecule, as such, is excluded, because all the evidence goes to show that this molecule is absent in mixed acids. Both the mixed anhydride and nitrogen pentoxide are almost certainly ionised in solution in sulphuric acid, as is shown by the cathode migration on electrolysis of a solution of nitrogen pentoxide in oleum (see following paper). The interpretation of Klemenc and Schöller's result must be that, in sulphuric acid, ionisation of nitrogen pentoxide produces the same nitrating entity as ionisation of nitric acid.

The NO_2^+ *ion.* We have shown that in mixed acids nitric acid is largely present in the form of the NO_2^+ ion characterised by a strong Raman shift $\Delta\nu = 1400$ cm.$^{-1}$. That this is also the nitrating agent in mixed acids may be argued as follows.

From Chédin's results we know approximate values for the limiting acid compositions in which the line 1400 cm.$^{-1}$ is just observable. These limiting compositions, shown as line *A* in the figure, may be compared with those which are effective in nitration. Hetherington and Masson (*loc. cit.*) have established that only mixed acids with compositions surpassing certain "threshold" values are capable of nitrating nitrobenzene, when the reaction is performed in the ordinary way, in a two-phase system at 35°. Their limiting compositions are shown as line *B* in the triangular diagram, representing mixed acid compositions in terms of mole fractions. Acid compositions within the triangle to the left of line *B* do not nitrate nitrobenzene; in those to the left of line *A* the concentration of line NO_2^+ ion must fall rapidly to zero. The two lines lie close together, indicating that the NO_2^+ ion is the nitrating agent for nitrobenzene.

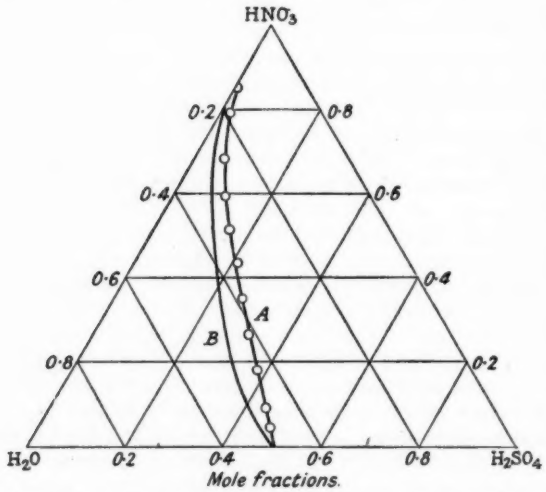
According to these views, the function of sulphuric acid in nitrating acid is to furnish a strongly acid medium, towards which nitric acid acts as a base, forming the reactive NO_2^+ ion by equation (5) (p. 870). This will be the most active nitrating agent present, but it is not necessarily required for the nitration of *all*

* Cf., *e.g.*, the results of Hetherington and Masson (*J.*, 1933, 105) for nitrobenzene (Fig. 1). In preparative, "two-phase" nitration, increasing solubility of organic matter in the acid phase and also the high proportion of nitric acid generally employed make it advantageous to use nitrating acids with as low a proportion of water as possible. For nitration in homogeneous solution, with a low proportion of nitric acid, the nitration rate is at a maximum in media in which the molar ratio $H_2O/H_2SO_4 \sim 0{\cdot}5$ (at 90°). These points will be discussed in later papers.

aromatic compounds. An easily nitrated substance may be nitrated by the NO_2·OH molecule. Thus, phenols can be nitrated by dilute aqueous nitric acid, and benzene is nitrated by acid compositions lying to the left of the limiting lines (see figure) (Lewis and Suen, *Ind. Eng. Chem.*, 1940, **32**, 1095). Nor is the action of the Hantzsch ions $H_2NO_3^+$ and $H_3NO_3^{++}$ excluded in all circumstances, if their existence is established.

Under the dehydrating conditions prevailing in mixed acids of low water content, or in oleum media, the NO_2^+ ion seems, however, to be formed; and whatever other possible nitrating agents are present, this may be assumed to be the most active one. This is in accord with the electronic theory of reactions, which postulates that a nitrating agent for the benzene ring is " cationoid," or " electrophilic," and is generally of the form X·NO_2, where X is an electron-attracting group (Benford and Ingold, *loc. cit.*). The effectiveness will depend upon the degree of electron attraction exerted by X upon the NO_2 group of the nitrating agent, which may thus be the positive end of a partly polarised molecule. It is logical to infer that the most active of all nitrating agents would be the NO_2^+ ion, carrying an integral positive charge.

The idea that a cation derived from nitric acid is the most effective nitrating constituent of mixed acids arises naturally from the electronic theory, but is not in itself new. Von Euler (*Z. angew. Chem.*, 1922, **35**, 580) supposed that sulphuric acid converted nitric acid into the NO_2^+ ion, the active nitrating agent. Walden (*ibid.*, 1924, **37**, 390), quoting a suggestion by Lother Meyer (" Grundzüge der theoretischen Chemie," Leipzig, 1890, pp. 173, 196), imagined the nitration of benzene by nitric acid as the reaction C_6H_5·H + HO^- + NO_2^+ = H_2O + C_6H_5·NO_2. Brewin and Turner (*J.*, 1928, 334) suggested the ion $N(OH)_4^+$ as the nitrating agent and, more recently, nitration by a cation has been discussed by Robinson (*J.*, 1941, 238; see also Ri and Eyring, *J. Chem. Physics*, 1940, **8**, 433; Westheimer and Kharasch, *loc. cit.*). Hantzsch's evidence for the existence of nitric acid cations has been used as a basis for suggestions that these are the nitrating agents by Youle (Thesis, Univ. of Sheffield, 1937), by Benford and Ingold (*loc. cit.*), by Lauer and Oda (*J. pr. Chem.*, 1936, **144**, 176), by Lantz (*Bull. Soc. chim.*, 1939, **6**, 302), and particularly by Ussanowitsch (*J. Gen. Chem. Russ.*, 1940, **10**, 219; cf. Williams, *Trans. Faraday Soc.*, 1941, **37**, 746). A quantitative formulation, hitherto lacking, can now be given as a result of kinetic experiments upon the nitration of 2 : 4-dinitrotoluene, nitrobenzene, *p*-chloronitrobenzene, and phenyltrimethylammonium nitrate in sulphuric acid–water mixtures. The hypothesis of exclusive nitration of these compounds by the cation (as against the assumption by Lantz and by Lauer and Oda that the cation nitrates only in anhydrous, or nearly anhydrous sulphuric acid, the NO_2·OH molecule being responsible for nitration in more aqueous media) not only explains the fundamental function of sulphuric acid as a nitration medium, but also accounts for Martinsen's discovery (*Z. physikal. Chem.*, 1904, **50**, 385; 1907, **59**, 605) that nitration is fastest in a medium of 91—92% sulphuric acid and not in anhydrous sulphuric acid or oleum. The effects of nitrous acid and added salts upon nitration speed are accounted for quantitatively. These experiments will be described in later papers.



Raman frequency $\Delta\nu$ 1400 *cm.*$^{-1}$ *observed only from line* A *to right.*
Nitration of nitrobenzene proceeds only to right of line B.

Appendix : Critical Examination of the Nitrogen Pentoxide Hypothesis.

The idea represented by equation (1) (p. 870), that nitrogen pentoxide is formed in concentrated mixed acid, owes its inception to Saposchnikov (*loc. cit.*) who made the first measurements of vapour pressure of the system. His results agree qualitatively with the more recent determinations by Berl, Andress, and Escales (*Kunststoffe*, 1937, **27**, 23) and by Vandoni (*loc. cit.*). The partial pressure of nitric acid is a maximum over mixtures of equal mole fraction of water and sulphuric acid, and declines to zero above solutions having a large excess of water or sulphuric acid owing to immobilisation of the nitric acid as nitrate or nitronium (NO_2^+) ion, respectively.

Progressive addition of sulphuric acid to aqueous nitric acid thus produces first a rise and then a fall of partial pressure of nitric acid. The initial rise was explained correctly by Saposchnikov to result from displacement by the sulphuric acid of molecular nitric acid from its hydrates; he tried, however, to account also for the subsequent fall in partial pressure in terms of the dehydrating property of the sulphuric acid, which here might extract water from the nitric acid itself, leaving nitrogen pentoxide. Saposchnikov used the equation $2HNO_3 + nH_2SO_4 = N_2O_5 + H_2O,nH_2SO_4$, and claimed in support that the vapour of certain acid-rich mixtures contained nitrogen pentoxide. This claim is still quoted as an experimental justification of the nitrogen pentoxide hypothesis, but is mistaken. Distillation of concentrated mixed acid below 30° provides pure, absolute nitric acid (free from any anhydride), and is the method commonly used for its preparation. Above 30° the product is anhydrous nitric acid mixed with some nitrogen dioxide formed by its

thermal decomposition (Pascal and Garnier, *Ann. Chim.*, 1921, **15**, 253; Berl and Samtleben, *Z. angew. Chem.*, 1922, **35**, 201, 206). It is likely that Saposchnikov was misled by this decomposition. He determined vapour pressure by drawing a current of air through the mixed acid at 25°, the volatile product being absorbed in potash, weighed and analysed by a method which estimates both nitric and nitrous acids together. After certain experiments of long duration, the vapour was richer in nitrogen than nitric acid (22·2% of N), and this was attributed to admixture with nitrogen pentoxide (25·9% of N). Retrospectively, there is little doubt that the vapour was in fact that of nitric acid mixed with nitrogen dioxide (30·4% of N), formed by decomposition of the acid during the protracted experiment. Scrutiny of Saposchnikov's results shows that, of 16 acids examined having a higher mole fraction of sulphuric acid than of water, *five*, distributed at random, possessed an abnormal vapour which in *two* cases was richer in nitrogen even than nitrogen pentoxide. The original evidence of the occurrence of nitrogen pentoxide in the vapour of mixed acid is therefore slender; facts which refute its presence are now overwhelming.

Since the nitrogen pentoxide hypothesis was thus based on inconclusive experiments, it may be examined upon its logical merits. The chemistry of nitrogen pentoxide was obscure at the time of Saposchnikov. The compound is more volatile than nitric acid, straightforward dehydration of which would lead to a several-fold increase in total pressure (Russ and Pokorny, *Monatsh.*, 1913, **34**, 1027; Daniels and Bright, *J. Amer. Chem. Soc.*, 1922, **42**, 1131). Thus in the interpretation of their measurements by Berl and others, and by Vandoni, it is assumed that the pentoxide formed within the solution combines there with molecules of the medium. Berl concludes that combination takes place between nitrogen pentoxide and remaining molecular nitric acid: these form an involatile complex, $(HNO_3)_6,N_2O_5$, whose existence he had assumed earlier to account for the properties of mixtures of nitrogen pentoxide in nitric acid (nitric acid oleum). Vandoni, unable to find evidence for this compound, supposes that the nitrogen pentoxide unites with molecular sulphuric acid to form the complex N_2O_5,H_2SO_4. Each of these explanations is somewhat formal and mechanical, but that of Vandoni expresses the same idea as our own (namely, that nitric and sulphuric acids interact with the elimination of a molecule of water), and evidence is considered in para. 3, b which sustains the proposal that the ion of nitric acid in mixed acid is also a component of " nitric acid oleum."

Another objection may be raised to the suggestion that concentrated mixed acids contain nitrogen pentoxide, even in small proportion in equilibrium with one or other of the complexes above. Nitric acid dissolved in sulphuric acid is quite stable, whereas it is certain that a solution containing molecules of nitrogen pentoxide would decompose (Lueck, *J. Amer. Chem. Soc.*, 1922, **44**, 757; Eyring and Daniels, *ibid.*, 1930, **52**, 1472, 1486). The exact form of Berl's explanation may thus be discarded, since nitric acid oleum decomposes, more slowly but in the manner of a solution of nitrogen pentoxide in an inert solvent.

Our thanks are due to Professor W. E. Garner, F.R.S., and Professor E. L. Hirst, F.R.S., in whose laboratory the work described in this and the two following papers was begun, and to the Chief Scientific Officer of the Ministry of Supply for permission to publish the results.

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189. *Nitration in Sulphuric Acid. Part II. Migration of Nitric Acid to the Cathode during Electrolysis in Oleum Solution.*

By G. M. Bennett, J. C. D. Brand, and Gwyn Williams.

Analysis of the various parts of a solution of nitric acid in oleum of up to 18% SO_3 content, after electrolysis, shows that there is a general migration of nitric acid towards the cathode accompanied by some reduction at this electrode. Experiments in which barium is also present show that in a 16—18% oleum the nitric acid has a mobility of between 2 and 4 times that of the barium ion.

Experiments are also described on the electrolysis of solutions of nitrous acid and of nitrogen pentoxide in oleum and of nitric acid in 98·7% sulphuric acid.

Hantzsch (*Ber.*, 1925, **58**, 941) tried to prove the presence of the nitracidium cations in mixed acids (in which the molar ratio $H_2SO_4/H_2O>1$) by migration experiments similar to those which were successful for the nitracidium perchlorates in nitromethane (Hantzsch and Berger, *Ber.*, 1928, **61**, 1328). He says (*loc. cit.*, p. 961): " Experiments for the electrolytic detection of the nitronium (nitracidium) cation have already been undertaken, by the electrolysis of solutions of nitric acid in sulphuric acid, in which the nitric acid should migrate to the cathode. However, these experiments have for the present remained unsuccessful, for the sulphuric acid alone was decomposed—probably because the decomposition potential of the sulphurylium sulphate present in the sulphuric acid is smaller than that of the nitronium sulphate." His observations were confirmed by one of us in collaboration with Miss S. Ram in 1935. It is true that reduction of the sulphuric (and nitric) acids occurs at the cathode, but the passage quoted seems to confuse the electrode processes with the transport in the body of the electrolyte. More recently it seemed to us that, apart from the complication of reduction taking place at the cathode, the detection of the movement of a nitric acid cation in electrolysis was probably prevented by the presence in solution of the OH_3^+ ion. This ion would have great mobility and would consequently carry a large share of the current, so that the movement of the nitric cation might be obscured or

appear reversed. It seemed, therefore, that a solution of nitric acid in an oleum of moderate sulphur trioxide content might be a better subject for investigation. The use of oleum as medium has the further advantage that sulphur trioxide is reduced preferentially at the cathode and so furnishes partial protection for the nitric acid.

Experimental.

Materials.—Oleum media were prepared by distilling sulphur trioxide from commercial oleum into sulphuric acid, followed by one or more redistillations. Media were analysed for sulphur trioxide content by titration with water (Brand, this vol., p. 585). Anhydrous nitric acid was made by distilling 70% nitric acid from 98% sulphuric acid at 15 mm. Nitrogen pentoxide was made by distillation of a mixture of anhydrous nitric acid and phosphoric oxide.

Apparatus.—The first experiments were made with a Pyrex U-tube fitted with ground glass stoppers, each carrying (*a*) an outlet tube leading to a sulphuric acid bubbler, and (*b*) the sealed-in platinum leads to the electrodes. These were of smooth platinum, each formed of a horizontal spiral of stout wire (area 1·23 sq. cm.), situated not more than 1 mm. below the meniscus of the electrolyte. Several experiments in which platinised platinum electrodes were used showed so great an increase in the reduction of both nitric and sulphuric acids at the cathode that this type of electrode was abandoned. The U-tube was cooled by immersion in running water at room temperature. After electrolysis, one or more samples were pipetted from the vertical limbs of the U-tube and the residue was poured from the horizontal portion. Pipette samples were always taken from the extreme upper layer of liquid, so that the first samples to be extracted (usually 2 c.c.) contained the liquid nearest to the electrodes. Products and losses due to electrode decomposition were generally concentrated in these. In later experiments (from No. 24 onwards) a more detailed record of the final distribution of solute was obtained by using a W-tube, composed of three vertical limbs (" cathode," " centre," and " anode " in the tables) connected by two horizontal portions. The two extreme vertical limbs carried the electrodes and outlet tubes; the central limb was stoppered. With this apparatus, successive samples were pipetted from the vertical limbs and, finally, two intermediate samples (" cathode middle " and " anode middle ") were taken by pouring the liquid which remained (after withdrawing the electrode and middle samples) simultaneously from the two ends of the apparatus.

Analysis.—In all samples, the nitric acid was determined, usually by the nitrometer, any nitrous acid formed by reduction being thus included. In a number of experiments, electrometric titration by ferrous sulphate (Treadwell and Vontobel, *Helv. Chim. Acta*, 1937, **20**, 573) was used to estimate nitric acid alone. When large differences between the results of these two methods revealed the presence of nitrous acid, this was often estimated by ceric sulphate.

Sulphur dioxide formed by cathode reduction interfered with the nitrometer analysis. After a number of experiments this was found to be removable by potassium permanganate. Using a freshly made solution of permanganate in 50% sulphuric acid, it was found that sulphur dioxide present in a sample would not reduce it rapidly if the concentration of the sample was more than 60% H_2SO_4. The first method adopted therefore involved cautious addition of water to the sample in an ice-cooled stoppered tube until the 60% concentration was reached, followed by permanganate in 50% acid drop by drop until a permanent pink colour remained. The sample was then washed into the nitrometer with concentrated sulphuric acid, and the analysis completed as usual. This procedure was in general satisfactory, but the addition of water to an oleum containing more than about 10% of sulphur trioxide caused some loss of nitrous fumes with a consequent error of up to 2% on the result for the nitric acid content.

The second method, suitable for oleums strong in sulphur trioxide, was to remove the sulphur dioxide by adding just enough finely powdered solid potassium permanganate directly to the oleum samples before introduction into the nitrometer, and to shake until the smell of sulphur dioxide disappeared (cf. Lunge and Keane, " Technical Methods of Chemical Analysis," 1908, Vol. I, p. 345). Too great an excess of permanganate interferes with the reaction in the nitrometer, but tests showed that up to 2 mg. of this salt may be added to each g. of oleum without affecting the volume of nitric oxide subsequently developed; and this quantity is enough to destroy the sulphur dioxide in the cathode limb of a typical migration experiment. For example, in analysing a solution of nitric acid in 18% oleum, 1-c.c. samples gave the following volumes (in c.c.) of nitric oxide at N.T.P. :

(1) With no SO_2 present	16·34	(3) SO_2 present (no $KMnO_4$ treatment)	16·6
(2) With 2—3 mg. $KMnO_4$ added (no SO_2)	16·37	(4) Sample (3) with added $KMnO_4$	16·35

Cathode Reduction.—Losses of nitric acid were of two kinds : (*a*) due to formation of gaseous nitrogen oxides, lost to subsequent analysis; (*b*) due to reduction to nitrous acid, included in the nitrometer analysis and sometimes estimated separately. (*a*) The total balance of nitrogen acid revealed a small loss which increased with the time of electrolysis and with the current strength. With oleums of higher sulphur trioxide content the loss of nitrogen acid was less, the reduction of sulphur trioxide to sulphur dioxide then taking precedence. Nitrous fumes were sometimes visible escaping from the solution at the cathode, and frequently white crystals of nitrosylsulphuric acid were deposited on the wall of the tube above the catholyte. As a result of the cathode processes a small volume of electrolyte near the cathode was always distinguishable as having a different density and refractive index and, sometimes, as no longer fuming. This part of the electrolyte had usually a pink or mulberry colour, probably caused by the presence of traces of iron and the reaction of these with nitrous acid. The colour could be reduced or eliminated by taking extreme precautions, redistilling the oleum repeatedly and excluding all dust.

It was found best to remove this coloured layer completely and separately as one sample, since it carried almost the whole of the cathode loss; a second sample then represented the normal cathode concentration. Much of the loss from the solution occurred as nitric oxide. After reaction with air in the apparatus, this was absorbed by the sulphuric acid bubbler and could be estimated by the nitrometer. (*b*) Appreciable amounts of nitrous acid (as nitrosyl sulphate), formed by reduction of nitric acid at the cathode, were also retained within the solution and could be estimated by direct analysis (see Table IV). Conversion into nitrous acid was small in experiments conducted in media containing 17—18% of sulphur trioxide, amounting then to about 5 moles-% of the nitric acid originally present. Here again reduction centres upon the sulphur trioxide of the medium; and the quantity of nitrous acid formed consequently increases if a solution of nitric acid is electrolysed in a weaker oleum or in concentrated sulphuric acid.

A smell of ozone was obvious at the anode and peroxidic substances were formed there.

Electrolysis of Solutions containing Barium.—The nitric acid was determined, as usual, with the nitrometer : the barium by diluting the sample and collecting the precipitated sulphate in a porous porcelain crucible and igniting at 800°. The precipitates, which were of about 10 mg., were weighed on a Sartorius micro-balance.

Electrolysis of Oleum containing s-Trinitrobenzene.—In the course of experiments aimed at checking whether the observed migration of nitric acid was real or due to a contrary motion of the medium, trinitrobenzene was chosen as an inert solute, known from the cryoscopic evidence not to produce ions in sulphuric acid. Unfortunately, this substance is decomposed by oxidation at the anode and is therefore not a satisfactory neutral indicator; nevertheless, the experiment, upon examination, has significance.

Solutions of trinitrobenzene in oleum were electrolysed for 5 hours with a current of 0·06 amp., and the liquid then

taken for analysis in several divisions. The organic matter in each sample was determined by dilution, extraction with benzene, and evaporation and weighing of the residue. Nitric acid was also determined. The results are summarised in Table I.

TABLE I.

Electrolysis of s-*Trinitrobenzene in* 13·7% *Oleum.* (Time : 5 hrs. Current : 0·06 amp.)

	Concn., mol./l., of :	Original solution.	After electrolysis. Cathode.	Cathode middle.	Centre.	Anode middle.	Anode.
Expt. 26.	T.N.B.	0·435	0·445	0·430	0·439	0·386	0·387
	HNO_3	0	0·010	0·019	0·008	0·099	0·101
	[T.N.B.] + [HNO_3]/3	0·435	0·448	0·436	0·442	0·419	0·421
Expt. 27.	T.N.B.	0·464	0·464	0·462	—	0·431	0·419
	HNO_3	0	0·026	0·014	—	0·075	0·108
	[T.N.B.] + [HNO_3]/3	0·464	0·473	0·467	—	0·457	0·455

Calculation shows (1) that 3 moles of nitric acid appear for each mole of trinitrobenzene lost, and (2) that a total balance of 99·7% of the original trinitrobenzene is accounted for if allowance is made for that which produces nitric acid. It is, moreover, apparent that destruction of the trinitrobenzene occurs at the anode and that nitric acid has spread from that end of the solution towards the cathode. The last line of figures for each experiment gives a corrected concentration of trinitrobenzene, and this shows a rise at the cathode and a fall at the anode amounting, in each instance, to 2—3%. It is evident, however, that some of this apparent movement may be due to migration of the nitric acid liberated at the anode, so that the figure of 2—3% represents an upper limit to the possible transport of sulphuric acid under consideration. A comparison of this result with those of the experiments with nitric acid shows that the migration of nitric acid observed (Tables II—IV) was several times greater than this maximum effect of movement of sulphuric acid. The electrolysis of a solution containing both the indicator substance and the nitric acid, which would be the best evidence, could not be conclusive here in view of the confusion arising between nitric acid from the trinitrobenzene indicator and the nitric acid added as solute.

DISCUSSION OF RESULTS.

Table II gives full particulars of the experimental conditions, with results in terms of the volume of nitric oxide evolved from 1-c.c. or 2-c.c. samples after electrolysis.

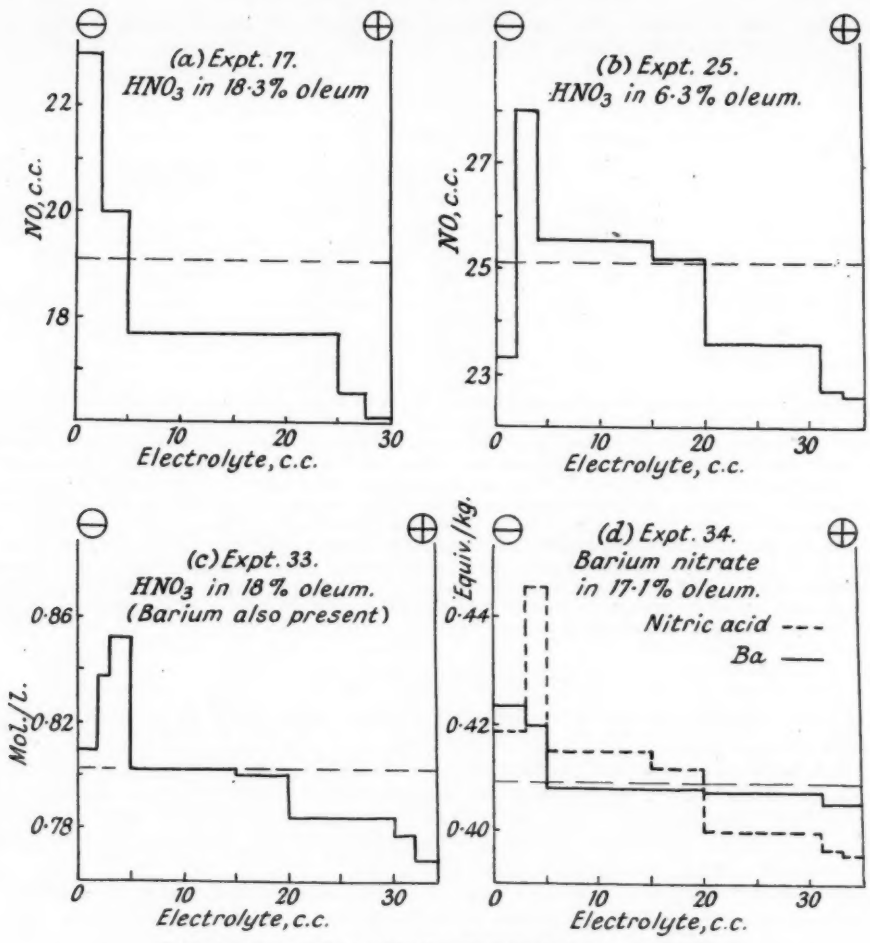
The results, essentially the same with both types of apparatus, are most easily appreciated graphically. Examples are shown in the figure, representing the distribution of nitric acid after electrolysis of originally homogeneous solutions. Apart from a fall due to loss by reduction to gaseous products in the immediate neighbourhood of the cathode (seen best in the W-tube experiments), there is a general accumulation of nitrogen acids at the cathode and a deficit at the anode after electrolysis.

It is necessary, however, to prove that the observed movement of nitrogen acid from anode to cathode is real and not merely an apparent migration caused by transport of other components in the opposite direction. For this purpose it would be desirable to repeat the migration experiments in presence of a solute known to be a non-electrolyte in oleum, since any change of concentration of such a material after electrolysis would be due to migration of the solvent. But to find a substance which is a non-electrolyte in oleum solution and is also chemically stable to oleum (and preferably to nitric acid as well) is not easy. Some experiments with *s*-trinitrobenzene have been referred to in the experimental section. Satisfactory results were obtained by carrying out simultaneous migrations of nitric acid and of the barium ion.

Hammett and Lowenheim (*J. Amer. Chem. Soc.*, 1934, **56**, 2620; cf. Riesenfeld and Feld, *Z. Elektrochem.*, 1920, **26**, 286; Meyer and Friedrich, *Z. physikal. Chem.*, 1922, **101**, 498) studied the electrolysis of barium sulphate in anhydrous sulphuric acid. Using trichloroacetic acid as a neutral indicator substance, they found a small but real migration of barium into the cathode compartment. They measured an apparent transport number $n_e = 0{\cdot}012$ for the barium ion, which fell to 0·007 after correction for movement of the medium; and they concluded that conduction must be largely by the proton-jump mechanism (Grotthuss conduction), which means that transfer of solvent molecules will be correspondingly small. Although this in itself makes it unlikely that our observed migration of nitric acid towards the cathode could be entirely caused by solvent movements, we have nevertheless used the barium ion as an indicator in further migration experiments in which barium and nitric acid were simultaneously present in oleum solution.

The results are given in Table III. Expt. 28 confirms the small cathode migration of the barium ion on electrolysis of a solution of barium sulphate in oleum. The remaining experiments in this table were performed with solutions prepared by dissolving barium nitrate in oleum; and the distribution of barium after electrolysis was determined gravimetrically. The results show (cf. section *d* of figure) that, during electrolysis, migration of nitrogen acid is 2—4 times more pronounced than that of barium (cf. Table V). Since barium is known to undergo a real migration, the reality of the nitric acid migration is thus confirmed.

It may still be objected that the nitrometer method of analysis records both nitric and nitrous acids and it remains to be proved that the observed migration is in fact migration of *nitric acid*. To test this point, samples after electrolysis were divided and analysed (*a*) for total nitrogen acids by nitrometer, (*b*) for nitric acid by electrometric titration with ferrous sulphate, (*c*) for nitrous acid by quantitative oxidation with ceric sulphate. The results are given in Table IV, which includes a number of duplicate analyses to show the reproducibility of the experiments.



Distribution of nitric acid after electrolysis in oleum solution.
Horizontal broken line : Solution before electrolysis.
In (a) *and* (b) *ordinates show c.c. of* NO *given by 2 c.c. of electrolyte.*

TABLE II.

*Electrolysis of Solutions of Nitric Acid in Oleum.**

Expt. No.	Medium, % SO_3.	HNO_3, mol./l.	Time, hrs.	N Acids recovery, %.	Original solution.	C.c. of NO at N.T.P. from 2 c.c. of electrolyte. After electrolysis : Cathode. I.	Cathode. II.	Cathode middle.	Centre.	Anode middle.	Anode. I.	Anode. II.
A. *Solution prepared from oleum and anhydrous nitric acid.*												
14	4·5	0·414	5	95	18·2		18·8	—	17·5	—		16·7
15	18·3	0·427	5	97	19·1		19·4	—	18·4	—		18·0
17	18·3	0·427	21	96	19·1	23·0	20·0	—	17·7	—	16·6	16·1
21	9·6	0·357	20·5	92	15·97	16·77	16·81	—	14·38	—	14·18	14·09
22	9·6	0·357	10	96	15·97	18·49	17·03	—	15·37	—	15·00	14·86
24	6·3	0·560	10	98	25·05	25·25	28·23	26·08	24·41	23·00	23·03	23·51
25	6·3	0·560	7	98	25·05	23·31	27·99	25·54	25·20	23·58	22·75	22·61
B. *Solution prepared by dissolving barium nitrate in oleum.*												
C.c. of NO at N.T.P. from 1 c.c. of electrolyte.												
31	16	0·805	6·8	99·8	18·03		18·67	18·30	18·04	17·69		17·46
32	18·1	0·832	6·75	99·4	18·46	18·19	18·97	18·78	18·47	17·98	17·95	17·58
33	18·3	0·803	6·7	99·5	18·02	18·2 18·8	19·1	17·93	17·90	17·58	17·45	17·21
C. *Solution of nitrogen pentoxide in oleum.*												
42	16·9	—	7·3	99·5	12·90	14·1	13·21	13·06	12·82	12·60	12·31	12·17
					12·97			12·92	12·83	12·70		

* The current was 0·06 amp. except for Expts. 14 and 15, where it was 0·1 amp., and Expt. 17, where it was 0·07 amp.

TABLE III.

*Electrolysis of Solutions of Barium Sulphate and Nitric Acid in Oleum.**

Expt. No.	Medium, % SO_3.	Solute, mol./kg.	Time, hrs.		Recovery, %.	Original solution.	Analysis of samples of electrolyte (mol./kg.). After electrolysis. Cathode. I.	Cathode. II.	Cathode middle.	Centre.	Anode middle.	Anode.
28	13·6	0·247 $BaSO_4$	5	Barium	100·1	0·2470	0·2511		0·2473	0·2468	0·2468	0·2465
30	16	0·219 $Ba(NO_3)_2$	6·9	Barium N-acid	— —	0·2217 0·443	0·2259 0·459		0·2230 0·441	0·2226 0·440	Deposition of solid prevented analysis	
34	17·1	0·205 $Ba(NO_3)_2$	7·2	Barium N-acid	99·96 99·7	0·2044 0·410	0·2119 0·419	0·2102 0·446	0·2040 0·415	0·2040 0·412	0·2038 0·400	0·2028 0·397, 0·396
35†	18·2	0·190 $Ba(NO_3)_2$	7·5	Barium N-acid	99·95 99·5	0·190 0·395	0·1951 0·400	0·1920 0·423	0·1902 0·400	0·1900 0·393	0·1892 0·384	0·1874 0·379

* The current in each experiment was 0·06 amp.

† Owing to a defect in the nitrometer, the analyses for N-acids in Expt. 35 are high throughout by approximately 3%.

TABLE IV.

Expt. No.	Medium.	Time, hrs.*		Recovery, %.	Original solution.	Analysis of samples of electrolyte (mol./l.). After electrolysis. Cathode. I.	Cathode. II.	Cathode middle.	Centre.	Anode middle.	Anode. I.	Anode. II.
Electrolysis of nitric acid solutions.												
41	SO_3 17·1%	7·6	N-acids	99·5	0·645	0·658	0·699	0·649	0·643	0·628	0·618	0·614
			HNO_3	94·8	0·642	0·300	0·61	0·648	0·633	0·630	—	0·610
			HNO_2		0·0	(0·358)	(0·09)	(0)	(0)	(0)	(0)	(0)
37	H_2SO_4 98·7%	8·5	N-acids	96·5	0·649	0·473	0·633	0·664	0·651	0·648	0·618	0·592
					0·650			0·670	0·651	0·652		
									0·657	0·658		
38	H_2SO_4 98·7%	8·5	N-acids	97·5	0·662	0·578	0·654	0·678	0·660	0·657	0·613	0·595
					0·666			0·673	0·662	0·658		
					0·663							
			HNO_3	66	0·671	0·027	0·286	0·405	0·553	0·556	0·612	—
			HNO_2	31	0·0	0·556	(0·366)	0·259	0·098	0·187	(0)	—
								0·262				
Electrolysis of nitrosyl sulphate in oleum.												
39	SO_3 18%	17·9	N-acids	99·7	0·615	0·660	0·632	0·625	0·618	0·596	0·581	0·575
								0·630	0·611	0·592		
40	SO_3 17·1%	19·2	N-acids	98·6	0·517	0·578	0·536	0·512	0·499	0·484	0·484	0·478
					0·508			0·520	0·494	0·485		
					0·512							
			HNO_3	49	0·0	0·062	0·145	0·044	0·440	0·482		
			HNO_2	49		(0·578)	(0·474)	0·362	—	0·041	—	

Note.—HNO_2 concentrations in parentheses are determined by difference, not by direct analysis for HNO_2.

* The currents were: Expts. 37 and 38, 0·07 amp.; Expts. 39 and 40, 0·05 amp.; Expt. 41, 0·06 amp.

Experiment 41 is conclusive for electrolysis in oleum solution. It shows, as usual, a deficit of nitrogen acid at the anode and an increment at the cathode, less marked in the sample " Cathode I " withdrawn from the immediate vicinity of the cathode than for " Cathode II," taken from a layer of liquid not immediately touching the cathode, because of cathode reduction of nitric acid to gaseous products which are lost. But the significant feature of the experiment is that, after electrolysis, nitrous acid is present only in the cathode limb and mainly in the sample " Cathode I," drawn from the immediate vicinity of the electrode. No nitrous acid is found in other parts of the apparatus.

It must therefore be *nitric acid* which migrates from anode to cathode, to suffer partial reduction at the cathode. Taken together with the final distributions observed in the other migrations, the result of Expt. 41 also disposes of the alternative supposition that destruction of nitric acid at the cathode is the prime cause, and that compensatory thermal diffusion sets up the inequalities of concentration observed after electrolysis. This supposition cannot be maintained, because it would require a deficit in the middle instead of at the anode, where it is found; and could not account for the increment observed in the cathode limb in samples not drawn from the immediate neighbourhood of the cathode.

The results of Tables II—IV therefore prove that, in oleum solution, nitric acid migrates from anode to cathode during electrolysis; and must exist in oleum solution in the form of a cation. The experimental arrangement is not sufficiently elaborate for the measurement of transport numbers; but it is useful to compare quantitatively the extent of transport of the nitro-cation with that of the barium ion under the same conditions. In Table V calculations are given for the transport of both ions from the anode in the W-tube experiments.

TABLE V.

Transport of Barium and Nitric Acid from the Anode in Oleum.

Expt. No.	Solute. Substance.	Concn.	Medium, % SO_3.	Transport, in equiv./Faraday. HNO_3.	Ba.
25	HNO_3	0·560 mol./l.	6·3	0·034	—
28	$BaSO_4$	0·247 mol./kg.	13·6	—	0·008
30	$Ba(NO_3)_2$	0·219 mol./kg.	16·0	Anode not analysed	0·007
31	$Ba(NO_3)_2$	0·402 mol./l.	16·0	0·019	Not analysed
32	$Ba(NO_3)_2$	0·412 mol./l.	18·1	0·022	,,
33	$Ba(NO_3)_2$	0·401 mol./l.	18·3	0·019	,,
34	$Ba(NO_3)_2$	0·205 mol./kg.	17·1	0·021	0·007
35	$Ba(NO_3)_2$	0·190 mol./kg.	18·2	0·022	0·004
38	HNO_3	0·663 mol./l.	98·7% H_2SO_4	0·014	—
40	$Ba(NO_3)_2$	0·322 mol./l.	16·9	0·018	Not analysed
42	N_2O_5	{0·577 equiv./l. 0·288 mol./l.	16·9	0·016	—

In competitive experiments, the cation of nitric acid in oleums of sulphur trioxide content of 16—18% has a mobility of 2—4 times that of the barium ion.

Migration in Concentrated Sulphuric Acid.—It is obviously desirable to extend the proof of cathode migration of nitric acid from oleum media to concentrated sulphuric acid media, free from sulphur trioxide. The effect of electrolysing solutions of nitric acid in 98·7% sulphuric acid is shown in Table IV (Expts. 37 and 38). After electrolysis there is a marked fall in concentration of nitrogen acids in the anode limb and there is a general movement of such acid towards the cathode. But when sulphur trioxide is absent, nitric acid becomes the principal target for cathode reduction, as Hantzsch observed. Gaseous losses (mainly nitric oxide) at the cathode are greater than in oleum solutions, and cathode reduction to nitrous acid is so extensive and disturbing that nitrous acid becomes distributed, during electrolysis, as far as the " anode middle " section of the electrolyte (Expt. 38). Disregarding the cathode compartment, it is clear in both Expts. 37 and 38 that nitric acid migrates away from the anode. The extent of transport from the anode is comparable with that observed in oleum media (Table V, Expt. 38).

Migration of Nitrous Acid in Oleum Media (cf. Angus and Leckie, *Trans. Faraday Soc.*, 1935, **31**, 958).—For comparison with the experiments of the preceding paragraph, nitrosyl sulphate was electrolysed in 18—19% oleum (Table IV). Migration of nitrogen acids from anode to cathode takes place, but only to about two-thirds of the extent observed with nitric acid in a similar medium. At the same time, anodic oxidation of nitrous acid to nitric acid is very great (after electrolysis the anode limb contains 94 mol.-% of nitric acid) and nitric acid is found even in the cathode limb (Expt. 40). The experiments give no clear evidence about the electrolytic migration of the NO^+ ion and it might even be argued that the greater part of the current is carried by the nitric acid cation.

Migration of Nitrogen Pentoxide in Oleum Medium.—When electrolysed in oleum solution, nitrogen pentoxide migrates from anode to cathode (Table II, C). The nitrogen pentoxide employed contained 94% (w/w) of N_2O_5, the remainder being N_2O_4. Migration of the impurity is quite insufficient to account for the effect observed. The transport is comparable in magnitude (Table V) with that observed for nitric acid in oleum. After electrolysis, 99·5% of the initial material is accounted for by the nitrometer analyses, so loss of gaseous reduction products is negligible. This result, indicating that nitrogen pentoxide ionises in oleum, has an obvious bearing upon the discussion in the preceding paper of the supposed formation of nitrogen pentoxide in mixed acids.

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190. *Nitration in Sulphuric Acid. Part III. The Influence of Nitric Acid and Other Substances upon the Oleum–Water Titration.*

By JOHN C. D. BRAND.

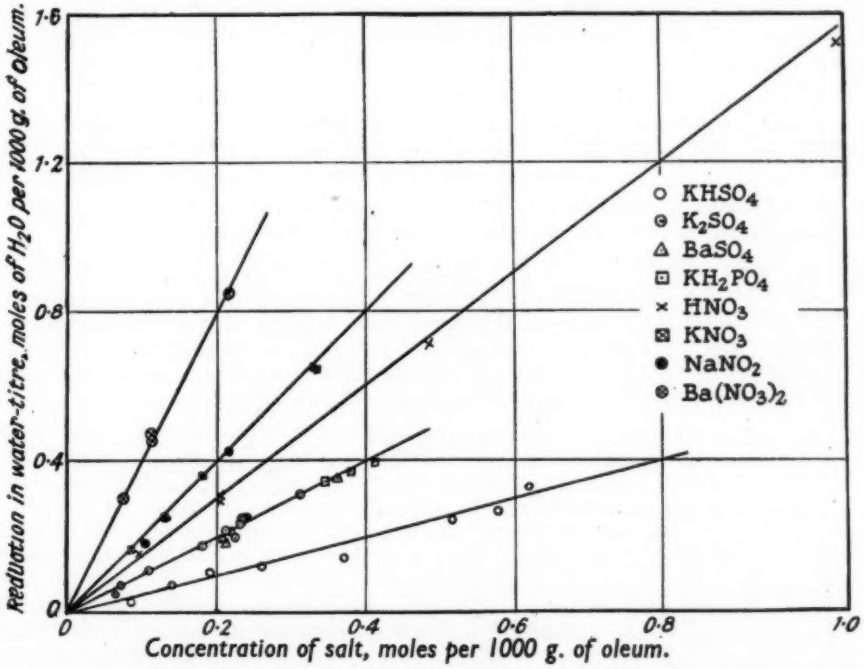
The water titration of oleum (Brand, this vol., p. 585) has been carried out in presence of various added substances. The solutes fall into several groups with respect to their effect in reducing the observed water-titre of the oleum. The reduction in moles of water required per mole of solute added is: (1) for two aromatic trinitro-compounds, none; (2) for potassium hydrogen sulphate, 0·5 mole; (3) for potassium and barium sulphates, 1 mole; (4) for nitric acid, 1·5 moles; (5) for potassium nitrate and sodium nitrite, 2 moles; and (6) for barium nitrate, 4 moles.

These results are shown to be consistent with the reactions $HNO_3 + 2H_2SO_4 \longrightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$ and $HNO_2 + 2H_2SO_4 \longrightarrow NO^+ + H_3O^+ + 2HSO_4^-$. The effect of the bisulphate ion is discussed in terms of the ionic equilibria in the oleum solution.

THE liberation of water when nitric acid dissolves in sulphuric acid is shown in a direct and simple manner by experiments based on the fact that sulphur trioxide in excess of the composition H_2SO_4 may be titrated by adding water to oleum until fuming just ceases (Brand, *loc. cit.*); " free " sulphur trioxide is thus determined with an uncertainty of about one part in 100 parts.

For the present purpose, titrations have been made with specimens of oleum to which various amounts of a number of solutes have been added (see Table I). All the substances tested, except the two trinitro-compounds, caused a diminution in the amount of water required for the titration of the oleum; this diminution was proportional to the amount of solute added, and independent of the initial sulphur trioxide concentration in the oleum (although the *total* water-titre necessarily varied with the strength of the oleum used). The two organic compounds had a negligible effect.

The solution for each titration was made up by weight, and the solute concentration expressed as molalities (moles of solute per 1000 g. of solvent oleum). Each titration was calculated in terms of the number of moles of water which must be added, per 1000 g. of solvent, to the solution in order to produce a mixture which does not fume. It is supposed that 1000 g. of oleum, either alone or as solvent, will require the same volume of water for titration provided there is no reaction between oleum and solute in the latter case. As explained, however,



addition of a solute usually diminishes the titration of the solvent: the diminution, in moles of water, is compared with the solute concentration in cols. 2 and 1 of Table I. It is found that these two quantities are directly proportional to one another (Table I, cols. 3—4) and, for each substance, the proportionality constant is either integral or half-integral. That this is true is appreciated from the figure, in which the lines are drawn to be of definite slopes (½, 1, 1½, 2, and 4) rather than through the points which group about them.

The results may be summarised as follows: the solutes fall into groups in their effects in reducing the water-titre of oleum, the reduction (in moles of water per mole of solute added) being (1) for the trinitro-compounds, nil; (2) for potassium hydrogen sulphate, 0·5; (3) for potassium and barium sulphates and potassium dihydrogen phosphate, 1·0; (4) for nitric acid, 1·5; (5) for potassium nitrate and sodium nitrite, 2; (6) for barium nitrate, 4.

Discussion of Results.—Diminution of the water-titration means that the addition of solute to an oleum removes some of the " free " sulphur trioxide, presumably by chemical combination with it. The number of moles of water by which the titre of a solution is depressed below that of the pure oleum clearly equals the number of moles of sulphur trioxide which have combined chemically with the solute. The results show that this quantity is in a simple ratio to the solute concentration. It is therefore an experimental fact that, when added to oleum, one mole of bisulphate combines with 0·5 mole of sulphur trioxide. The interpretation of this fact is discussed on p. 882. If this be accepted, the remaining results are consistent if (*a*) one mole of nitric acid or nitrous acid causes the disappearance of 1·5 moles of sulphur trioxide, and (*b*) one mole of orthophosphoric acid removes 0·5 mole of sulphur trioxide. Potassium sulphate dissolves in sulphuric acid as $2KHSO_4$, barium sulphate as $Ba(HSO_4)_2$, potassium nitrate yields $KHSO_4$ and HNO_3, sodium nitrite $NaHSO_4$ and HNO_2, barium nitrate $Ba(HSO_4)_2$ and $2HNO_3$, and potassium dihydrogen phosphate $KHSO_4$ and H_3PO_4. There is no reason to suspect that the inorganic cations present in the solution have any influence upon the water-titre.

TABLE I.

Diminution in Water-titre of Oleum caused by Addition of Solutes.

(a = Moles of solute added to 1000 g. of oleum; b = reduction in water-titre in moles per 1000 g. of oleum.)

Solute.	a.	b.	b/a.	Mean.*	Solute.	a.	b.	b/a.	Mean.*
2 : 4 : 6-Trinitro-toluene	0·135	0·000	0	0	$BaSO_4$	0·214	0·183	0·86	0·96
						0·362	0·367	1·02	
1 : 3 : 5-Trinitro-benzene	0·178	0·033	0·17	0·05	KH_2PO_4	0·208	0·194	0·93	
	0·460	0·006	0·01			0·218	0·211	0·97	
$KHSO_4$	0·087	0·028	0·32			0·347	0·345	0·99	0·97
	0·141	0·072	0·51			0·385	0·372	0·97	
	0·191	0·106	0·56			0·413	0·400	0·97	
	0·261	0·122	0·47	0·48	HNO_3	0·096	0·155	1·61	
	0·372	0·144	0·39			0·205	0·294	1·43	
	0·517	0·245	0·47			0·205	0·311	1·52	1·47
	0·578	0·267	0·46			0·486	0·711	1·46	
	0·621	0·333	0·54			1·042	1·52	1·46	
K_2SO_4	0·065	0·050	0·8		KNO_3	0·086	0·168	1·95	
	0·073	0·072	0·99			0·182	0·364	2·00	1·96
	0·110	0·111	1·01			0·332	0·651	1·96	
	0·182	0·178	0·98			0·334	0·650	1·95	
	0·213	0·216	1·01	0·99	$NaNO_2$	0·105	0·183	1·74	
	0·225	0·200	0·89			0·131	0·250	1·91	1·94
	0·231	0·233	1·01			0·218	0·427	1·96	
	0·235	0·250	1·06		$Ba(NO_3)_2$	0·075	0·300	4·00	
	0·241	0·250	1·04			0·113	0·472	4·18	4·00
	0·313	0·311	0·99			0·114	0·456	4·00	
						0·217	0·849	3·91	

* The mean quotients for each series are calculated by dividing the sum of the figures of col. 2 by the sum of those of col. 1, thus giving increasing weight to the results obtained at higher concentrations.

The inference (a) above answers the question about the state adopted by nitric acid in oleum solution. Some of the possible equations representing the supposed behaviour of nitric acid in sulphuric acid are given in Table II, together with the number of moles of sulphur trioxide which should consequently be used up when the solvent is an oleum. The experimental results support equation (5) consistently. If the mixed anhydride in equation (2) is imagined to be ionised, then this equation becomes (5). As mentioned in Parts I and II, there is evidence that nitrogen pentoxide ionises when dissolved in oleum.

TABLE II.

Reaction.	Moles of SO_3 taken up from oleum by 1 mole of HNO_3.
(1) $2HNO_3 = N_2O_5 + H_2O$	0·5
(2) $HNO_3 + H_2SO_4 = NO_2{\cdot}O{\cdot}SO_3H + H_2O$	1·0
(3) $HNO_3 + H_2SO_4 = H_2NO_3^+ + HSO_4^-$	0·5
(4) $HNO_3 + 2H_2SO_4 = H_3NO_3^{++} + 2HSO_4^-$	1·0
(5) $HNO_3 + H_2SO_4 = NO_2^+ + HSO_4^- + H_2O$.....	1·5

The results with sodium nitrite give an independent demonstration of the conversion of nitrous acid by sulphuric acid into nitrosyl and bisulphate ions (cf. Part I); and it follows from inference (b) that orthophosphoric acid dissolves in sulphuric acid to react as follows: $H_3PO_4 + H_2SO_4 = P(OH)_4^+ + HSO_4^-$, requiring in oleum, 0·5 mole of sulphur trioxide per mole of orthophosphoric acid. A phosphacidium perchlorate $[P(OH)_4^+][ClO_4^-]$ has been prepared by Arlman (*Rec. Trav. chim.*, 1937, **56**, 919). The cryoscopic behaviour of potassium dihydrogen phosphate in sulphuric acid is quite different from that of potassium nitrate (cf. Part I), a much smaller value for the i factor being obtained (Hantzsch, *Z. physikal. Chem.*, 1909, **65**, 41), and the effect of orthophosphoric acid upon the rate of decomposition of malic acid in anhydrous sulphuric acid (Dittmar, *J. Amer. Chem. Soc.*, 1930, **52**, 2746) also suggests that each molecule of the acid yields one bisulphate ion in this medium. It is possible that ionisation of nitric acid proceeds through the comparable Hantzsch ion $NO(OH)_2^+$ (whose anion immobilises 0·5 mole of SO_3, cf. Table II) and that this is at once dehydrated to NO_2^+ by the sulphuric acid medium.

The Influence of Bisulphate Ion upon the Water-titration of Oleum.—To interpret the reaction between nitric acid and oleum it was necessary to use, but not to explain, the experimentally observed effect of bisulphate ion upon the water-titration. The end-point of the titration is marked by the cessation of fume. It is assumed that fuming is a property of un-ionised pyrosulphuric acid, a fraction of which dissociates into sulphur trioxide and H_2SO_4 (see Part I; cf. Miles, Niblock, and Wilson, *Trans. Faraday Soc.*, 1940, **36**, 345; Miles, Niblock, and Smith, *ibid.*, 1944, **40**, 281). The solid salts of pyrosulphuric acid have no tendency to lose sulphur trioxide in the cold: it is therefore assumed that the ions $HS_2O_7^-$ and $S_2O_7^{--}$ do not, *of themselves*, give rise to fume.

To explain the influence of bisulphate ions upon the fuming of oleum it is necessary to suppose further that, in sulphuric acid, pyrosulphuric acid is moderately acidic in its first ionisation. The argument is as follows: if pyrosulphuric acid is stronger than sulphuric acid an added bisulphate will be converted into hydrogen pyrosulphate ion by the equilibrium

$$HSO_4^- + H_2S_2O_7 \rightleftharpoons HS_2O_7^- + H_2SO_4 \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Were pyrosulphuric acid weak in its behaviour, solvolysis of the ion $HS_2O_7^-$ (equilibrium 6, reading from right to left) would be considerable, always affording sufficient molecular pyrosulphuric acid for fuming to be perceptible, and the titration of the solution would not differ from that of the oleum alone save in the sharpness of the end-point. In practice a diminution is observed. On the other hand, were pyrosulphuric acid to ionise in sulphuric acid as a strong acid, a bisulphate dissolved in a solution containing an excess of pyrosulphuric acid would be transformed quantitatively into acid pyrosulphate, solvolysis of the ion $HS_2O_7^-$ being zero or negligible. This would lead to cessation of fuming when the solution contained one mole of " free " sulphur trioxide per mole of added potassium (or other) hydrogen sulphate, the solutes being present entirely as $HS_2O_7^-$ ions. In fact, the titration is diminished by one-half of this amount, presumably because the acidity of pyrosulphuric acid is between the two extremes chosen for illustration.

The effect of a bisulphate upon the water-titration is summed up by the statement that the addition of $2A$ moles of potassium or another hydrogen sulphate to oleum containing A moles of " free " sulphur trioxide checks the fuming exactly. The result is accounted for if the solution at the end-point contains equal concentrations of $KHSO_4$ and KHS_2O_7 (A moles of each), or if it contains $K_2S_2O_7$ (A moles). The gulf between these two views is smaller than it appears. If the latter view, which accounts immediately for the simple arithmetical ratio encountered, is correct, the second ionisation of pyrosulphuric acid cannot be immoderately weak, permitting the existence of $S_2O_7^{--}$ ions in solutions containing very little or no molecular pyrosulphuric acid. Solvolysis of the ion $S_2O_7^{--}$ (see 7) must be greater proportionately than that of the ion $HS_2O_7^-$,

$$S_2O_7^{--} + H_2SO_4 \rightleftharpoons HS_2O_7^- + HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad (7)$$

whose reaction with the solvent (see 6) is small but perceptible. However, molecular pyrosulphuric acid would only be formed from $S_2O_7^{--}$ ions by co-operation of the simultaneous equilibria (6) and (7), which (by the present hypothesis) combine to be unfavourable to its formation, and consequently its concentration would be too minute for fuming to be observed. A solution of potassium hydrogen sulphate ($2A$ moles) in oleum containing an equivalent amount of " free " sulphur trioxide ($2A$ moles) fumes because solvolysis of the KHS_2O_7 produces $H_2S_2O_7$ in one stage. Fuming diminishes on adding water. The addition of A moles of water would convert the KHS_2O_7 ($2A$ moles) approximately into $K_2S_2O_7$ (A moles), reducing the concentration of molecular pyrosulphuric acid to a second order of smallness. Fuming would cease at this point.

The alternative view is that the exactly titrated solution contains an equal concentration of hydrogen sulphate and hydrogen pyrosulphate ions, and its implication is that the second ionisation of pyrosulphuric acid is insignificantly weak. Accordingly, complete solvolysis would befall the ion $S_2O_7^{--}$ in sulphuric acid. This picture differs, therefore, from that offered previously in supposing that equilibrium (7) lies on the right rather than on the left. The accompanying argument interprets the position of the end-point as follows: the fuming of solutions of bisulphate in oleum is supposed to become imperceptible when titration has reduced the concentration of molecular pyrosulphuric acid to a critical concentration C, which should be the same however much bisulphate was dissolved initially, and must be very small. In the final stages of titration pyrosulphuric acid is furnished by adjustment of equilibrium (6); if K be the mass-action constant of this equilibrium, the concentration of molecular pyrosulphuric acid (ignoring changes in the concentration of H_2SO_4) is given by $[H_2S_2O_7] = [HS_2O_7^-]/K[HSO_4^-]$. Provided that K be sufficiently large, this relation accounts for the experimental fact that fuming always ceases ($[H_2S_2O_7] = C$) at the same ratio of the molar concentrations of " free " sulphur trioxide and bisulphate ion, but the interpretation accepts as a coincidence the fact that this ratio is half-integral. It is improbable that the concentration of molecular pyrosulphuric acid left unobserved at the end of a titration could exceed 0·001 molal, and, therefore, because at this point the concentrations of $HS_2O_7^-$ and HSO_4^- ions are equal, the hypotheses of this paragraph yield a figure of $K > 10^3$ for the constant of equilibrium (6). This figure would describe the acidity of pyrosulphuric acid to a better approximation than previous statements.

It will be apparent that the alternative hypotheses which have been discussed reduce to extreme opposite points of view regarding the position of equilibrium in equation (7). An intermediate condition is also possible, the exact solution requiring further data.

Experimental.

Materials.—The purification and titration of oleum are described elsewhere (Brand, *loc. cit.*). The method of preparation of anhydrous nitric acid (99·9% HNO_3) is referred to in Part II. The inorganic salts chosen as solutes were of A.R. purity.

Method.—The strength of the oleum in which the compounds named in Table I were dissolved and titrated varied

Table III.

Oleum.		Potassium nitrate.		Water-titration.		Diminution of water-titre, molality.
SO_3, %.	Wt. used, g.	Wt. used, g.	Molality.	Obs., ml.	Molality.	
17·0	23·40	—	—	0·895	2·127	—
	28·94	1·010	0·334	0·770	1·477	0·650
11·4	21·72	—	—	0·554	1·417	—
	25·84	—	—	0·659	1·417	—
	23·19	—	—	0·595	1·425	—
	24·75	0·216	0·086	0·558	1·252	0·168
	25·34	0·468	0·182	0·482	1·056	0·364
	25·28	0·849	0·332	0·350	0·769	0·651

between 5% and 18% of " free " sulphur trioxide. Titrations were made upon samples of 20—50 g., and were reproducible to about 1%. The diminution of titration observed in presence of a solute was subject, therefore, to a greater error than this; the error, moreover, increases with the initial strength of the solvent oleum at a given solute concentration, and, for solutions in a given oleum, rises rapidly with diminishing concentration of substance dissolved. Upon analysis of the results of Table I, it is found that the figures of col. 3 seldom differ by more than the accepted vagary of experiment from the integral or half-integral ratios given in col. 4. Table III contains detailed results of the titration of potassium nitrate in oleum : it is apparent that the lowering of titration produced by this salt does not depend upon the initial strength of the solvent, and that the molar lowering has a value which is double the solute concentration within the error of experiment outlined above.

These experiments were undertaken at the suggestion of Professor G. M. Bennett and are published by permission of the Chief Scientific Officer of the Ministry of Supply, to both of whom the author wishes to convey his thanks.

KING'S COLLEGE, LONDON. [*Received, March 7th,* 1946.]

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191. *New Syntheses of Heterocyclic Compounds. Part VII.* 9-*Amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrenes.*

VLADIMIR A. PETROW.

A new method for the synthesis of some 9-amino-6 : 8-dimethyl-7 : 10-diazaphenanthrenes from *o*-nitroaryl aldehydes has been developed.

Condensation of *o*-nitrobenzaldehyde with β-aminocrotononitrile and ethyl β-aminocrotonate led to the formation of *ethyl* 3-*cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* (III; R = CO_2Et). Oxidation of this gave *ethyl* 3-*cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylate* (IV; R = CO_2Et), hydrolysed to the corresponding *acid* (IV; R = CO_2H), and decarboxylated to 3-*cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine* (IV; R = H). Reduction of this compound was accompanied by cyclisation and formation of 9-*amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VIII; R = H). The constitution assigned to this compound was confirmed by reaction with nitrous acid to give 9-*hydroxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VII), identical with the *lactam* formed by reduction of *ethyl* 4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine*-3-*carboxylate* (VI; R = H).

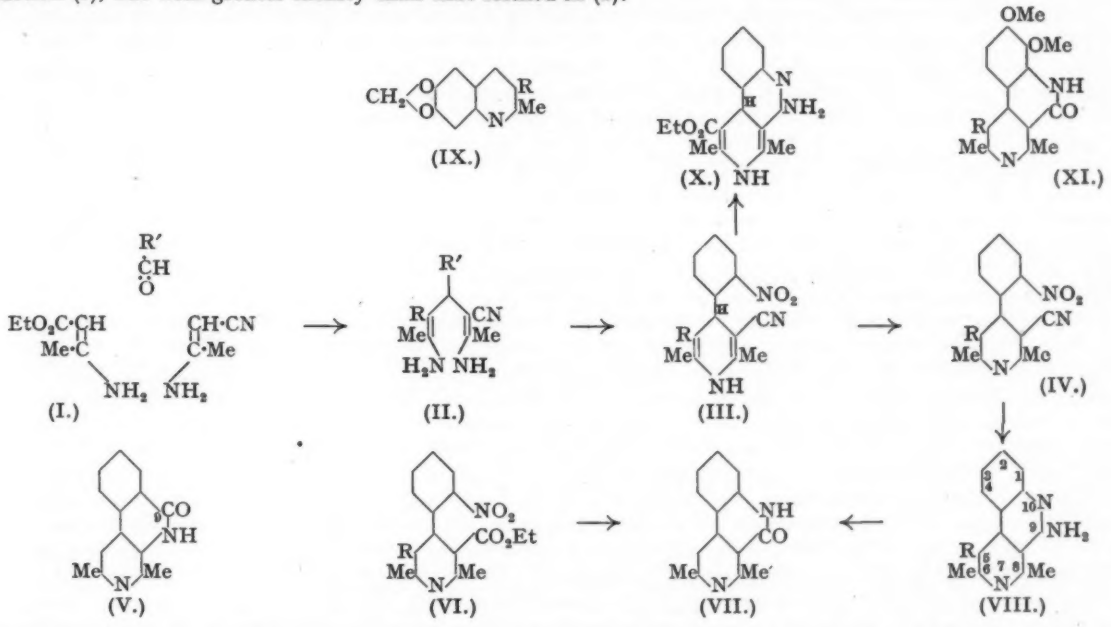
The synthesis has been applied to 6-nitropiperonal and to 2-nitrovanillin, leading to the formation of 9-*amino*-2 : 3-*methylenedioxy*- and 9-*amino*-1 : 2-*dimethoxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* respectively.

EARLIER work on the relationship between structure and biological activity in the diazaphenanthrene (benznaphthyridine) series (Part V, Petrow, this vol., p. 200; see also footnote on nomenclature, *ibid.*, p. 201) has now been extended to some derivatives of the hitherto unknown 7 : 10-diazaphenanthrene. These were prepared by a method involving several novel features. In the first place, a new extension of Hantzsch's collidine synthesis has been developed whereby 3-*cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridines* (*e.g.*, IV; R = H) are obtained. Secondly, the interesting observation has been made that reduction of these compounds is accompanied by cyclisation and formation of the 9-*amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrenes* (*e.g.*, VIII; R = H). Although rearrangements of this type have been employed in the pyridine and quinoline series (Meyer, *Zentr.*, 1908, ii, 591; Pschorr, *Ber.*, 1898, **31**, 1289; Tröger and Köppen-Kastrop, *J. pr. Chem.*, 1922, **104**, 335; Gabriel, *Ber.*, 1918, **51**, 1500), the literature apparently records only one instance of its application to the synthesis of an aminonaphthyridine, *viz.*, the condensation of cyanoacetic ester with 6 : 6′-diamino-3 : 4 : 3′ : 4′-tetramethoxybenzophenone leading to the formation of an 8-amino-1-hydroxy-3 : 4 : 5 : 6-diveratro-2 : 7-naphthyridine (Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 630).

The well-known synthesis of pyridine derivatives by Hantzsch's method from two molecules of ethyl acetoacetate, one molecule of an aldehyde, and ammonia, was shown by Knoevenagel (*Ber.*, 1898, **31**, 738, cf. Beyer, *ibid.*, 1891, **24**, 1662) to take place through the intermediate formation of ethyl β-aminocrotonate. Further study of the reaction revealed that one molecule of ethyl acetoacetate could be replaced by such ketomethylene compounds as acetaldehyde (Michael, *Ber.*, 1885, **18**, 2020), desoxybenzoin (Knoevenagel, *Annalen*, 1894, **281**, 74), and β-diketones and their ammonia derivatives (Knoevenagel and Ruschaupt, *Ber.*, 1898, **31**, 1025). An extension of what is essentially the same reaction was independently discovered by Meyer (*J. pr. Chem.*, 1895, **52**, 101), who replaced the ethyl β-aminocrotonate by β-aminocrotononitrile. In this way a wide variety of dicyanodihydropyridines was prepared by Mohr (*ibid.*, 1897, **56**, 124), and by Meyer (*ibid.*, 1908, **78**, 507; 1915, **92**, 175).

It appeared from these observations that a mixed Hantzsch–Knoevenagel reaction between an aldehyde, β-aminocrotononitrile, and ethyl β-aminocrotonate (I; see scheme) might be expected to occur with formation of a 4-*substituted ethyl* 3-*cyano*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* (*e.g.*, III; R = CO_2Et). Experimental study has now shown this to be the case. Slow condensation took place in the expected manner on heating the components in a solvent such as alcohol, with steady evolution of ammonia over periods of up to 60 hours. Occasionally reaction did not appear to proceed to completion with consequent difficulty in isolating the product. This was easily overcome by heating the reaction mixture, after removal of solvent, with acetic anhydride. These results may be interpreted by considering the reaction between an aldehyde and (*a*) β-aminocrotononitrile, or (*b*) ethyl β-aminocrotonate. Mohr (*loc. cit.*) has shown that in reaction (*a*) the 1 : 5-diamine (II; R = CN) is initially formed. Conversion of this compound into a dihydropyridine such as (III; R = CN) fails to take place on heating, but occurs readily on treatment with acidic reagents such as acetic anhydride. In contrast to this, reaction (*b*) proceeds to completion on simply heating the components

for a few hours on the water-bath (cf. Knoevenagel, 1898, *loc. cit.*). The condensation of an aryl aldehyde with equimolar amounts of β-aminocrotononitrile and ethyl β-aminocrotonate probably takes place through the 1 : 5-diamine (II; R = CO_2Et), which evidently undergoes ring closure less readily than the intermediate formed in reaction (*b*), but with greater facility than that formed in (*a*).



The above reaction has been successfully applied to a number of aromatic aldehydes (see Experimental), and the hitherto unknown ethyl cyanodihydropyridinecarboxylates obtained in yields varying from 15 to 70%. These products have been oxidised to the pyridines by dilute nitric acid in alcohol, or better by chromic acid in acetic acid (cf. also Part VIII, following paper).

When *o*-nitrobenzaldehyde was employed in this new synthesis, *ethyl* 3-*cyano*-4-o-*nitrophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* (III; R = CO_2Et) was obtained in 22% yield. Oxidation gave *ethyl* 3-*cyano*-4-o-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylate* (IV; R = CO_2Et), hydrolysed by one molecular proportion of potassium hydroxide in 50% alcohol to the corresponding *acid* (IV; R = CO_2H). On heating this acid above its melting point smooth decarboxylation occurred to give 3-*cyano*-4-o-*nitrophenyl*-2 : 6-*dimethylpyridine* (IV; R = H), characterised by its *picrate*. Reduction of the pyridine (IV; R = H) with reduced iron in aqueous alcohol containing a trace of hydrochloric acid was, in general, accompanied by rearrangement and formation of 9-*amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VIII; R = H). The product occasionally contained some uncyclised material, as shown by a positive primary amine test on diazotisation and coupling with alkaline β-naphthol. In these instances the crude reduction product was heated under reflux with sodium ethoxide to complete conversion of the cyano-amine into (VIII; R = H), which no longer gave the diazo-test (cf. however the behaviour of 8-amino-1-hydroxy-3 : 4 : 5 : 6-diveratro-2 : 7-naphthyridine on diazotisation, reported by Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 652). The constitution assigned to (VIII; R = H) was confirmed by preparation of a *benzoyl* derivative, and by reaction with nitrous acid, which gave 9-*hydroxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VII) in nearly quantitative yield. The formulation assigned to (VII) followed from its independent synthesis in the following way. Ethyl 4-*o*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (VI; R = CO_2Et) (Hinkel, Ayling, and Morgan, *J.*, 1931, 1837; cf. Lepetit, *Ber.*, 1887, **20**, 1341) was partially hydrolysed by one molecular proportion of potassium hydroxide in 50% alcohol to 3-*carbethoxy*-4-o-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylic acid* (VI; R = CO_2H). Decarboxylation of this acid-ester by heating above its melting point furnished the oily *ethyl* 4-o-*nitrophenyl*-2 : 6-*dimethylpyridine*-3-*carboxylate* (VI; R = H), characterised by its well-defined *picrate*. Reduction of this compound was accompanied by lactamisation and formation of 9-hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene (VII), identical in melting point and mixed melting point with the compound formed by the action of nitrous acid on (VIII; R = H).

6-Nitropiperonal condensed normally with β-aminocrotononitrile and ethyl β-aminocrotonate, and the resulting *ethyl* 3-*cyano*-4-(2′-*nitro*-4′ : 5′-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* was converted into 9-*amino*-6 : 8-*dimethyl*-2 : 3-*methylenedioxy*-7 : 10-*diazaphenanthrene*. An aminodiazaphenanthrene was not obtained when 6-aminopiperonal was employed in place of the nitro-aldehyde. Two substances were isolated from the complex reaction product after preliminary fractionation followed by treatment with acetic anhydride. The less soluble of the two was identified as 3-*cyano*-6 : 7-*methylenedioxy*-2-*methylquinoline* (IX; R = CN) by its direct synthesis from 6-aminopiperonal and β-aminocrotononitrile (cf.

Meyer, *J. pr. Chem.*, 1914, **90**, 1). The more soluble compound was the corresponding *ethyl* 6 : 7-*methylenedioxy*-2-*methylquinoline*-3-*carboxylate* (IX; R = CO_2Et), also obtained by the Friedländer method from 6-aminopiperonal and ethyl β-aminocrotonate. 6-Acetamidopiperonal failed to react in the synthesis and was largely recovered unchanged.

Although the condensation product of 2-nitrovanillin with β-aminocrotononitrile and ethyl β-aminocrotonate failed to crystallise, yet after acetylation *ethyl* 3-*cyano*-4-(2′-*nitro*-4′-*acetoxy*-3′-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* was readily isolated in 66% yield. Oxidation gave the corresponding *pyridine* derivative, also obtained together with an isomeric *nitro*-compound, by nitration of *ethyl* 3-*cyano*-4-(4′-*acetoxy*-3′-*methoxyphenyl*)-2 : 6-*dimethylpyridine*-5-*carboxylate*, prepared as above from vanillin. Previous experience in a related field (forthcoming publication) had shown that the decarboxylation of 4-hydroxyphenylpyridine-3-carboxylic acids was very unsatisfactory. *Ethyl* 3-*cyano*-4-(2′-*nitro*-4′-*hydroxy*-3′-*methoxyphenyl*)-2 : 6-*dimethylpyridine*-5-*carboxylate* was therefore prepared by hydrolysis of the above acetyl derivative, followed by methylation with methyl sulphate to the 4′-*methoxy*-derivative, and conversion of the latter without difficulty into 9-*amino*-1 : 2-*dimethoxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene*. The constitution assigned to this compound was supported by the action of nitrous acid on it to give 9-*hydroxy*-1 : 2-*dimethoxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (XI; R = H) in nearly quantitative yield.

Reduction of (III; R = CO_2Et) with reduced iron in faintly acid alcoholic solution gave a *product*, $C_{17}H_{19}O_2N_3$, which failed to give a positive primary amine test on diazotisation followed by coupling with alkaline β-naphthol, and must therefore be assigned the constitution of *ethyl* 9-*amino*-6 : 8-*dimethyl*-7 : 13-*dihydro*-7 : 10-*diazaphenanthrene*-5-*carboxylate* (X). Reduction of the appropriate pyridinecarboxylic esters (*e.g.*, IV; R = CO_2Et) likewise gave *ethyl* 9-*amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene*-5-*carboxylate* (VIII; R = CO_2Et), and *ethyl* 9-*amino*-2 : 3-*methylenedioxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene*-5-*carboxylate*, cyclisation of the intermediate amino-nitriles occurring in preference to lactamisation between the amino- and available carbethoxy-groupings. Reduction of ethyl 3-cyano-4-(2′-nitro-3′ : 4′-dimethoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate, on the other hand, led to the almost exclusive formation of the *lactam* (XI).

In Part V of this series (Petrow, *loc. cit.*) it was shown that the Schmidt rearrangement of 1 : 3-dimethyl-2-azafluorenone leads to a hydroxydimethyldiazaphenanthrene represented by either (V) or (VII). The constitution of 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (V) was assigned to this product, as oxidation of 1 : 3 : 9-trimethyl-2 : 10-diazaphenanthrene gave a hydroxydimethyl-2 : 10-diazaphenanthrene identical with it in melting point and mixed melting point. A direct comparison of the two sets of compounds derived from 2 : 10- and 7 : 10-diazaphenanthrene has now been made, and the results confirm the conclusions put forward in the earlier communication.

Experimental.

M. ps. are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

Ethyl 3-*Cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate* (III; R = CO_2Et).—*o*-Nitrobenzaldehyde (225 g.), β-aminocrotononitrile (125 g.), ethyl β-aminocrotonate (195 g.), and absolute alcohol (500 ml.) were heated under reflux for 70—80 hours; evolution of ammonia had then ceased. Light petroleum (300 ml., b. p. 40—60°) was added to the cooled mixture and, after several days at 0°, the crystalline product was collected and crystallised twice from aqueous methyl alcohol (charcoal). The *ester* formed lemon-yellow needles, m. p. 191·5—192·5° (Found: C, 62·5; H, 5·3; N, 12·7. $C_{17}H_{17}O_4N_3$ requires C, 62·4; H, 5·2; N, 12·8%). Yield, 107·5 g.

Ethyl 3-*Cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylate* (IV; R = CO_2Et).—The finely powdered dihydrobase (10 g.), suspended in absolute alcohol (40 ml.) was treated with dilute nitric acid (40 ml.; 1 part conc. acid : 7 parts water) on the water-bath. Vigorous reaction occurred and the material went into solution. The *product* was obtained crystalline by careful addition of dilute ammonium hydroxide in excess to the hot mixture. It formed glittering white needles from aqueous methyl alcohol, m. p. 115·5—116·5° (Found: C, 62·9; H, 4·6; N, 13·1. $C_{17}H_{15}O_4N_3$ requires C, 62·8; H, 4·6; N, 12·9%). Yield, 8·2 g. (85%).

3-*Cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylic Acid* (IV; R = CO_2H).—The corresponding ester (75 g.), potassium hydroxide (13·5 g.), absolute alcohol (150 ml.), and water (150 ml.) were heated under reflux for 80 hours. The alcohol was removed on the water-bath, the residue was diluted with water, and the filtered solution and washings were acidified by dropwise addition with stirring of dilute sulphuric acid (from 4·5 g. conc. acid). The precipitated acid formed a gelatinous mass which became crystalline on standing. It was collected, washed with water, and dried. Yield 20·3 g. (89%) of a *product*, m. p. 227—229°, which was pure enough for decarboxylation. It formed cubic crystals from aqueous alcohol, m. p. 232—233° (decomp.) (Found: C, 60·3; H, 3·8; N, 14·1. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1%).

3-*Cyano*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine* (IV; R = H).—The corresponding acid (8·4 g.) was heated in a metal-bath at 250—270° for 4—5 minutes; evolution of carbon dioxide had then ceased. The *product* was isolated by distillation under reduced pressure or by conversion into the picrate. It formed squat yellow needles from aqueous alcohol, m. p. 160·5—161·5° (Found: C, 66·5; H, 4·3; N, 16·4. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·3; N, 16·6%). Yield, 5·9 g. (80%). The *picrate* formed squat yellow needles from spirit, m. p. 216·5—217·5° (Found: N, 17·7. $C_{14}H_{11}O_2N_3,C_6H_3O_7N_3$ requires N, 17·4%).

9-*Amino*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VIII; R = H).—Crude 3-cyano-4-*o*-nitrophenyl-2 : 6-dimethylpyridine (2·8 g.), reduced iron (5·0 g.), water 5 ml.), spirit (30 ml.), and three drops of concentrated hydrochloric acid were heated under reflux for 2 hours. The mixture turned dark crimson and became gelatinous, but cleared after *ca.* 1½ hours. The mixture was filtered and the iron residues were thoroughly extracted with boiling spirit. The filtrate and washing were taken to dryness (m. p. 180—184°), and, as the primary amine test by diazotisation was still faintly positive, the product was heated under reflux with sodium ethoxide (1·2 g. of sodium in 50 ml. of alcohol) for 45 minutes. Water was added, the alcohol removed on the water-bath, and the *product* (m. p. 193—195°) crystallised from alcohol–ligroin (charcoal). It formed faintly yellow needles, m. p. 197—198° (Found: C, 75·3; H, 5·9; N, 19·0. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·8; N, 18·8%). Yield, 35—45%. The *picrate* separated from alcohol in pale yellow needles, m. p. 254—255° (decomp.) (Found: N, 18·7. $C_{14}H_{13}N_3,C_6H_3O_7N_3$ requires N, 18·6%). The base and picrate gave depressions of m. p. in admixture with the corresponding derivatives from 2 : 10-diazaphenanthrene described in Part V

(*loc. cit.*). 9-*Benzamido*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene*, obtained in nearly quantitative yield by treating the amino-compound (500 mg.) in pyridine (2·5 ml.) with benzoyl chloride (300 mg.) under reflux for 30 minutes, formed a felted mass of sparingly soluble silky white needles from spirit, m. p. 230—230·5° (Found : C, 76·9; H, 5·3; N, 13·2. $C_{21}H_{17}ON_3$ requires C, 77·2; H, 5·2; N, 12·8%).

9-*Hydroxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene* (VII).—(*a*) A solution of 9-amino-6 : 8-dimethyl-7 : 10-diazaphenanthrene (1·3 g.) in concentrated hydrochloric acid (3 ml.) and water (7 ml.) was cooled to 0° and a solution of sodium nitrite (700 mg.) in a little water slowly added with stirring. Rapid evolution of gas occurred and separation of crystalline material began after 1 minute. After 1 hour at room temperature, the mixture was heated on the water-bath for 30 minutes, made alkaline with ammonia, and the precipitated *base* collected and crystallised from spirit (charcoal). It separated in silky needles, m. p. 310—311° (Found : C, 74·8; H, 5·3; N, 12·6. $C_{14}H_{11}ON_3$ requires C, 75·0; H, 5·4; N, 12·5%). Yield, >90%. The compound gave a depression of m. p. in admixture with the corresponding 2 : 10-diazaphenanthrene compound described in Part V (*loc. cit.*).

(*b*) Ethyl 4-*o*-nitrophenyl-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate was prepared by the method of Hinkel, Ayling, and Morgan (*loc. cit.*). For oxidation, the finely powdered ester (22 g.) was added to chromic acid (4·1 g.) dissolved in a little water and glacial acetic acid (120 ml.), and the mixture heated on the water-bath for 10—15 minutes. The ester (VI; R = CO_2Et), precipitated in crystalline form by addition of dilute ammonia in slight excess, formed pale yellow needles from aqueous methyl alcohol, m. p. 92·5—93·5° (Found : C, 61·4; H, 5·4. Calc. for $C_{19}H_{20}O_6N_2$: C, 61·3; H, 5·4%) (Hinkel *et al.*, *ibid.*, p. 1839, give m. p. 75°). Yield, 19·7 g. 3-*Carbethoxy*-4-*o*-*nitrophenyl*-2 : 6-*dimethylpyridine*-5-*carboxylic acid* (VI; R = CO_2H), spear-head crystals from aqueous methyl alcohol, m. p. 216—217° (Found : C, 59·4; H, 4·7; N, 8·3. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%), was obtained by hydrolysis of the diethyl ester with 1 mol. of potassium hydroxide (10% solution in 50% alcohol) for 60 hours under reflux. Ethyl 4-*o*-nitrophenyl-2 : 6-dimethylpyridine-3-carboxylate (VI; R = H) was obtained in 70% yield as a pale yellow oil when the above acid-ester was heated for 5 minutes at 250—260°, and the product distilled under reduced pressure. The *picrate* separated from alcohol in fairly soluble bright yellow needles, m. p. 172—173° (Found : N, 13·5. $C_{16}H_{16}O_4N_2,C_6H_3O_7N_3$ requires N, 13·2%). The nitro-ester (3 g.) was reduced with reduced iron (6 g.), water (5 ml.), spirit (25 ml.), and 3 drops of concentrated hydrochloric acid for 50 minutes under reflux. The mixture was filtered and the iron residues were thoroughly extracted under reflux with successive large volumes of spirit. The filtrate and washings were taken to dryness and heated at 170° for 1 hour. This product, m. p. 310°, gave slightly low analyses for carbon (C, 74·5%). After sublimation at 270—280°/11 mm. and refluxing with acetic anhydride, 9-hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene (VII) formed silky white needles from spirit, m. p. 310—311° (Found : C, 74·7; H, 5·6; N, 12·4%), not depressed in admixture with the product obtained by method (*a*) above. Yield, 25%.

Ethyl 3-*Cyano*-4-(2′-*nitro*-4′ : 5′-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate*.—6-Nitropiperonal (115 g.), β-aminocrotononitrile (50 g.), ethyl β-aminocrotonate (78 g.), and absolute alcohol (400 ml.) were heated under reflux for 50 hours. The alcohol was removed under reduced pressure, the residue heated under reflux with 3 vols. of acetic anhydride for 10 minutes, and the mixture decomposed with water. The sticky brown product was collected, dried, heated under reflux with 5 vols. of benzene, and left at 0° for several days. The *product* was collected and crystallised twice from benzene (charcoal) and finally from methyl alcohol. It formed lemon-yellow octahedra, m. p. 224·5—225·5° (Found : C, 58·2; H, 4·6; N, 11·3. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·6; N, 11·3%). Yield, 35 g. (18%).

Ethyl 3-*cyano*-4-(2′-*nitro*-4′ : 5′-*methylenedioxyphenyl*)-2 : 6-*dimethylpyridine*-5-*carboxylate*, glittering needles from alcohol, m. p. 153—154° (Found : C, 58·7; H, 4·4; N, 11·3. $C_{18}H_{15}O_6N_3$ requires C, 58·5; H, 4·1; N, 11·4%), was prepared by suspending the finely powdered dihydro-ester (35 g.) in glacial acetic acid (90 ml.), adding a solution of chromic acid (7·5 g.) in a little water, and heating with shaking on a water-bath until a clear solution was obtained. Yield, 30 g. (85%).

3-*Cyano*-4-(2′-*nitro*-4′ : 5′-*methylenedioxyphenyl*)-2 : 6-*dimethylpyridine*.—The foregoing ester was hydrolysed and the crude acid (m. p. 145°) decarboxylated. The *product* formed faintly coloured plates from aqueous methyl alcohol, m. p. 173—174° (Found : C, 60·7; H, 3·8; N, 14·3. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1%). By reduction it gave 9-*amino*-2 : 3-*methylenedioxy*-6 : 8-*dimethyl*-7 : 10-*diazaphenanthrene*, glittering needles from aqueous alcohol, m. p. 228—228·5° (Found : C, 67·2; H, 4·9; N, 16·0. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%).

6-*Aminopiperonal Series*.—(*a*) 6-Aminopiperonal (10 g.), β-aminocrotononitrile (5 g.), ethyl β-aminocrotonate (8 g.), and absolute alcohol (25 ml.) were heated under reflux for 30 hours; evolution of ammonia had then ceased. After being allowed to cool, the product was collected (m. p. 150—170°, yield 12 g.) and crystallised from aqueous alcohol. The less soluble fraction (m. p. 185—195°) was heated under reflux with acetic anhydride for 15 minutes, the mixture decomposed with water, and the insoluble fraction crystallised from benzene–light petroleum. 3-*Cyano*-6 : 7-*methylenedioxy*-2-*methylquinoline* (IX; R = CN) formed small needles, m. p. 214—215° (Found : C, 68·2; H, 4·2; N, 13·1. $C_{12}H_8O_2N_2$ requires C, 67·9; H, 3·8; N, 13·2%). The more soluble fraction, m. p. 150—152°, after sublimation under reduced pressure and treatment with acetic anhydride, gave *ethyl* 6 : 7-*methylenedioxy*-2-*methylquinoline*-3-*carboxylate* (IX; R = CO_2Et), dazzling white plates from benzene–light petroleum, m. p. 159—160° (Found : C, 65·1; H, 5·1; N, 5·6. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%).

(*b*) 3-Cyano-6 : 7-methylenedioxy-2-methylquinoline, m. p. 214—215° (Found : N, 13·3%), not depressed in admixture with a sample prepared by method (*a*), was obtained in 60% yield by heating aminopiperonal (2·3 g.), β-aminocrotononitrile (2·3 g.), and absolute alcohol (10 ml.) for 40 hours under reflux.

(*c*) Ethyl 6 : 7-methylenedioxy-2-methylquinoline-3-carboxylate, m. p. 162—163° (Found : N, 5·6%), not depressed in admixture with a sample prepared by method (*a*), was obtained in 58% yield by heating aminopiperonal (1·65 g.), ethyl β-aminocrotonate (2·58 g.), and absolute alcohol (5 ml.) for 40 hours under reflux.

Ethyl 3-*Cyano*-4-(2′-*nitro*-4′-*acetoxy*-3′-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-5-*carboxylate*.—2-Nitrovanillin (400 g.) (Raiford and Sloesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2559), β-aminocrotononitrile (167 g.), ethyl β-aminocrotonate (262 g.), and absolute alcohol (1000 ml.) were heated under reflux for 74 hours. The product, after removal of solvent, was heated under reflux with acetic anhydride (1200 ml.) for 45 minutes, and the cooled product poured into water (7000 ml.) and shaken until decomposition was complete. The granular precipitated material was collected and crystallised from dilute acetic acid. The *ester* formed golden-yellow leaflets, m. p. 175—177° (Found : C, 57·2; H, 4·8; N, 11·2. $C_{20}H_{21}O_7N_3$ requires C, 57·8; H, 5·1; N, 10·1%). Yield, 560 g. (68%).

Ethyl 3-*cyano*-4-(2′-*nitro*-4′-*acetoxy*-3′-*methoxyphenyl*)-2 : 6-*dimethylpyridine*-5-*carboxylate*, pearly needles, m. p. 112—113° (Found : C, 57·7; H, 4·5; N, 10·0. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6; N, 10·2%), was prepared by gradually treating a hot solution of the above dihydro-base (120 g.) in glacial acetic acid (300 ml.) with chromic acid (25 g.) in water (100 ml.), and when oxidation was complete adding water to the hot mixture until crystallisation commenced. Yield, 64%.

Ethyl 3-*Cyano*-4-(2′-*nitro*-4′-*hydroxy*-3′-*methoxyphenyl*)-2 : 6-*dimethylpyridine*-5-*carboxylate*.—The foregoing acetyl derivative (80 g.), potassium hydroxide (20 g.), water (100 ml.), and alcohol (100 ml.) were heated under reflux for 40 minutes. The alcohol was removed on the water-bath, the mixture diluted to 400—500 ml., and the *base* precipitated

with glacial acetic acid (20 ml.). It formed squat glittering needles from aqueous methyl alcohol, m. p. 187·5—188·5° (Found : C, 58·6; H, 4·8; N, 11·0. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·6; N, 11·3%). Yield, nearly quantitative. A solution of the substance in dilute alcohol gave a purple coloration with ferric chloride solution.

Ethyl 3-Cyano-4-(2′-nitro-3′ : 4′-dimethoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate.—A solution of the above hydroxy-compound (37 g.) in potassium hydroxide (6·5 g.) and water (300—400 ml.) was treated at room temperature with shaking with methyl sulphate (12·6 g.) added over 45 minutes. After 24 hours at room temperature the product was collected. Passage of carbon dioxide through the filtrate precipitated unchanged material (*ca.* 10%). The *dimethoxy*-compound formed octahedra from aqueous alcohol, m. p. 131·5—132·5° (Found : C, 59·2; H, 5·0; N, 10·8. $C_{19}H_{19}O_6N_3$ requires C, 59·2; H, 4·9; N, 10·9%). Yield, 80%.

3-Cyano-4-(2′-nitro-3′ : 4′-dimethoxyphenyl)-2 : 6-dimethylpyridine.—The foregoing ester was hydrolysed and the crude acid (m. p. 195—205°) decarboxylated. The *product* formed glittering needles from benzene–ligroin, m. p. 182—183° (Found : C, 61·5; H, 5·1; N, 13·7. $C_{16}H_{15}O_4N_3$ requires C, 61·3; H, 4·8; N, 13·4%). The *picrate* formed rather soluble bright yellow needles from absolute alcohol, m. p. 190·5—191·5° (Found : N, 15·1. $C_{16}H_{15}O_4N_3,C_6H_3O_7N_3$ requires N, 15·5%).

9-Amino-1 : 2-dimethoxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene, glittering faintly yellow needles from benzene–ligroin, m. p. 183—184° (Found : C, 67·3; H, 6·0; N, 14·9. $C_{16}H_{17}O_2N_3$ requires C, 67·9; H, 6·0; N, 14·8%), was prepared by reduction of the foregoing nitro-compound. It was fairly soluble in water. On treatment with nitrous acid in hydrochloric acid solution it yielded *9-hydroxy-1 : 2-dimethoxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene* (XI; R = H), glittering plates from spirit, m. p. 242·5—243·5° (Found : C, 67·5; H, 5·8; N, 9·6. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6; N, 9·9%).

Ethyl 3-cyano-4-(4′-hydroxy-3′-methoxyphenyl)-2 : 6-dimethyl-1 : 4-dihydropyridine-5-carboxylate, faintly yellow spear-shaped crystals from aqueous alcohol, m. p. 161—162° (Found : C, 65·5; H, 6·3; N, 8·7. $C_{18}H_{20}O_4N_2$ requires C, 65·9; H, 6·1; N, 8·5%), was prepared from vanillin. Yield, 62%.

Ethyl 3-cyano-4-(4′-acetoxy-3′-methoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate, glistening plates from aqueous methyl alcohol, m. p. 165—166° (Found : C, 65·3; H, 5·6; N, 8·2. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·4; N, 7·6%), was prepared by acetylation of the foregoing hydroxy-compound followed by oxidation with chromic acid. Yield, 80%.

Nitration of Ethyl 3-Cyano-4-(4′-acetoxy-3′-methoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate.—The ester (10 g.) was added with mechanical stirring to fuming nitric acid (40 g.) cooled in ice-salt, over a period of 30 minutes. The product was poured on ice, made alkaline with ammonia, and the precipitated material collected and crystallised from aqueous methyl alcohol. The less soluble fraction gave *ethyl 3-cyano-4-(?′-nitro-4′-acetoxy-3′-methoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate*, flat pearly plates, m. p. 177—178° (Found : C, 57·8; H, 4·8; N, 10·2. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6; N, 10·2%). Yield, 10%. The more soluble fraction gave ethyl 3-cyano-4-(2′-nitro-4′-acetoxy-3′-methoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate, pearly needles, m. p. 112—113° (Found : C, 57·8; H, 4·8; N, 10·1%), not depressed in admixture with the compound prepared from 2-nitrovanillin (above). Yield, 10%.

Ethyl 3-cyano-4-(4′-hydroxy-3′-methoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate, prismatic needles from alcohol–ligroin, m. p. 132·5—133·5° (Found : C, 66·4; H, 5·5; N, 8·7. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6%), was prepared by hydrolysis of the corresponding acetyl derivative (20 g.), with potassium hydroxide (7 g.) and water (60 ml.) under reflux for 1 hour, followed by precipitation of the base with acetic acid (7 ml.).

Ethyl 3-cyano-4-(3′ : 4′-dimethoxyphenyl)-2 : 6-dimethyl-1 : 4-dihydropyridine-5-carboxylate, faintly yellow rhombic crystals from aqueous alcohol or ligroin, m. p. 166—167·5° (Found : C, 66·4; H, 6·5; N, 8·0. $C_{19}H_{22}O_4N_2$ requires C, 66·7; H, 6·4; N, 8·2%), was prepared from veratraldehyde followed by heating with acetic anhydride. Yield, 36%. Oxidation with chromic acid gave *ethyl 3-cyano-4-(3′ : 4′-dimethoxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate*, flat glittering needles from aqueous alcohol, m. p. 148—149° (Found : N, 8·3. $C_{19}H_{20}O_4N_2$ requires N, 8·2%).

Ethyl 3-Cyano-4-(3′ : 4′-methylenedioxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate.—As the product obtained from piperonal failed to crystallise, even after heating with acetic anhydride, it was oxidised with chromic acid without further treatment. Tedious fractionation from aqueous methyl alcohol and finally from benzene–ligroin, gave *ethyl 3-cyano-4-(3′ : 4′-methylenedioxyphenyl)-2 : 6-dimethylpyridine-5-carboxylate*, glistening needles, m. p. 132·5—133·5° (Found : C, 66·5; H, 5·1; N, 8·9. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 4·9; N, 8·6%). Yield, 10%. 2 : 4-Dinitrobenzaldehyde failed to react with β-aminocrotononitrile and ethyl β-aminocrotonate, and was recovered unchanged.

Ethyl 9-amino-6 : 8-dimethyl-7 : 13-dihydro-7 : 10-diazaphenanthrene-5-carboxylate (X), faintly yellow needles from alcohol–light petroleum, m. p. 164—165·5° (Found : C, 68·3; H, 6·3; N, 14·0. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%), was prepared by reduction of (III; R = CO_2Et) (1·4 g.) with reduced iron (2·5 g.), water (2·5 ml.), alcohol (6 ml.), and one drop of concentrated hydrochloric acid for 1 hour under reflux. Yield, 25%.

Ethyl 9-amino-6 : 8-dimethyl-7 : 10-diazaphenanthrene-5-carboxylate (VIII; R = CO_2Et), prepared by reduction of (IV; R = CO_2Et), formed faintly yellow needles from benzene–ligroin, m. p. 191·5—192·5° (Found : C, 68·6; H, 5·6; N, 14·3. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·8; N, 14·2%). Yield, 25%.

Ethyl 9-amino-2 : 3-methylenedioxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene-5-carboxylate formed pale yellow platelets, m. p. 239—240° (Found : C, 63·7; H, 5·1; N, 12·9. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0; N, 12·4%).

9-Hydroxy-5-cyano-1 : 2-dimethoxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene (XI; R = CN), formed faintly straw-coloured silky needles, m. p. 301—302° (Found : C, 66·0; H, 4·8; N, 13·9. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·9; N, 13·6%), very sparingly soluble in the usual solvents, more soluble in boiling glacial acetic acid, and readily soluble in hot nitrobenzene.

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, March 29th*, 1946.]

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192. *New Syntheses of Heterocyclic Compounds. Part VIII. The Schmidt Rearrangement of* 1 : 3-*Dimethyl-2-azafluorenones* (*continued*).

By VLADIMIR A. PETROW.

4-*Amino-*, 4-*benzamido-*, 4-carboxy-, 4-*carbethoxy-*, 7-*nitro-*, 7-*amino-*, 7-*benzamido-*, and 7-methoxy-1 : 3-dimethyl-2-azafluorenones have been submitted to the Schmidt reaction. Only the 4-carbethoxy-derivative (II; R = CO_2Et) underwent rearrangement to give *ethyl 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene-*

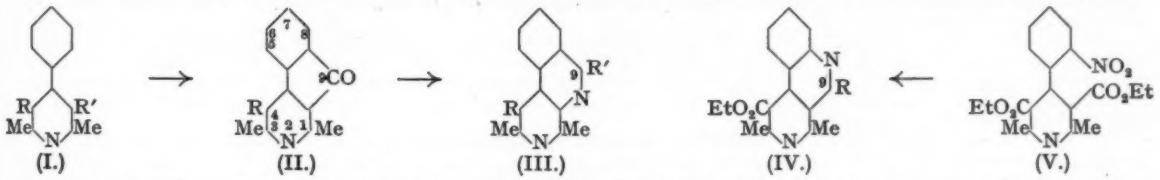
4-carboxylate (III; R = CO_2Et; R′ = OH), the constitution of which followed from its non-identity with the isomeric *ethyl 9-hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene-5-carboxylate* (IV; R = OH), obtained by reduction of ethyl 4-*o*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (V).

(III; R = CO_2Et; R′ = OH) has been converted into the *chloro*-compound (III; R = CO_2Et; R′ = Cl), and thence into *ethyl 9-amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene-4-carboxylate* (III; R = CO_2Et; R′ = NH_2).

In Part V of this series (Petrow, this vol., p. 200) it was reported that the Schmidt rearrangement of 1 : 3-dimethyl-2-azafluorenone (II; R = H) leads to the formation of 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (III; R = H; R′ = OH) in high yield. The investigation has been continued, and the present communication reports a study of the action of hydrazoic acid on a number of substituted 1 : 3-dimethyl-2-azafluorenones. Some of these have not hitherto been described in the literature, and were prepared as described below.

Nitration of 1 : 3-dimethyl-2-azafluorenone (II; R = H) gave a mono-nitro-derivative in excellent yield. From analogy with the formation of 2-nitrofluorenone from fluorenone by nitration under comparable conditions, this compound has been assigned the constitution of *7-nitro-1 : 3-dimethyl-2-azafluorenone*. Reduction gave *7-amino-1 : 3-dimethyl-2-azafluorenone*, characterised by its *benzoyl* derivative and *oxime*. The behaviour of this compound showed certain unusual features, perhaps associated with an " imine " type of structure. Thus it generally formed brilliant red micro-needles, m. p. 255°. When this red form was treated with stannous chloride in concentrated hydrochloric acid for 1½ hours on the water-bath, however, an unstable pink form, m. p. 225°, was obtained which gave the same bright yellow benzoyl derivative on benzoylation, and rapidly passed into the bright red form on further crystallisation. Again, it failed to give a positive primary amine test on diazotisation followed by coupling with alkaline β-naphthol. Attempts to prepare a benzylidene derivative gave inconclusive results. Finally, the benzoyl derivative failed to give a methosulphate on heating under reflux with methyl sulphate in nitrobenzene solution.

The isomeric *4-amino-1 : 3-dimethyl-2-azafluorenone* (II; R = NH_2) was prepared by application of the new synthetical method described in Part VII (preceding paper). Condensation of benzaldehyde with β-aminocrotononitrile and ethyl β-aminocrotonate led to the formation of *ethyl 5-cyano-4-phenyl-2 : 6-dimethyldihydro-*



pyridine-3-carboxylate in 67% yield, smoothly oxidised by dilute nitric acid to *ethyl 5-cyano-4-phenyl-2 : 6-dimethylpyridine-3-carboxylate* (I; R = CN; R′ = CO_2Et). Hydrolysis furnished the corresponding *acid* (I; R = CN; R′ = CO_2H), converted by concentrated sulphuric acid into *4-carbamyl-1: 3-dimethyl-2-azafluorenone* (II; R = $CO{\cdot}NH_2$). Hypobromite oxidation gave the bright red *4-amino-1 : 3-dimethyl-2-azafluorenone* (II; R = NH_2), characterised by its *oxime* and *benzoyl* derivative.

Partial hydrolysis of ethyl 4-phenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (I; R = R′ = CO_2Et) gave the mono-ester (I; R = CO_2Et; R′ = CO_2H) (Hantzsch, *Ber.*, 1884, **17**, 2910), converted by concentrated sulphuric acid into *ethyl 1 : 3-dimethyl-2-azafluorenone-4-carboxylate* (II; R = CO_2Et) in yields not exceeding 20%. This ester was better prepared when required in quantity by direct esterification of the readily accessible 1 : 3-dimethyl-2-azafluorenone-4-carboxylic acid (Mills, Palmer, and Tomkinson, *J.*, 1924, **125**, 2366) by the silver salt method. The remaining compound examined, 7-methoxy-1 : 3-dimethyl-2-azafluorenone, has been described by Borsche and Hahn (*Annalen*, 1939, **537**, 230).

The above derivatives of 1 : 3-dimethyl-2-azafluorenone failed to undergo the Schmidt rearrangement, with the exception of (II; R = CO_2Et), which gave an *ethyl 9-hydroxydiazaphenanthrenecarboxylate* in 35% yield. Although two structures (III; R = CO_2Et; R′ = OH) and (IV; R = OH) are clearly possible for this compound, the former is preferred from analogy with the Schmidt rearrangement of the parent ring system (II; R = H), which was shown in Part V (*loc. cit.*) to lead to the 2 : 10-diazaphenanthrene (III; R = H; R′ = OH). In contrast to (III; R = H; R′ = OH) this new carbethoxy-derivative was readily soluble in sodium hydroxide solution, from which it was precipitated by carbon dioxide. It formed a sparingly soluble bright yellow potassium salt, and failed to give a coloration with ferric chloride. Its formulation as *ethyl 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene-4-carboxylate* (III; R = CO_2Et; R′ = OH) followed, however, from its non-identity with authentic *ethyl 9-hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene-5-carboxylate* (IV; R = OH), obtained by reduction of ethyl 4-*o*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (V) with stannous chloride.

Now Kenner and Stubbings (*J.*, 1921, **119**, 602) have observed that although reduction of ethyl *oo′*-dinitrodiphenate leads to the formation of the corresponding dilactam, yet combustion analyses of this compound give figures consistently low for carbon and more in accord with its formulation as the corresponding diaminodiacid. Similar observations have been recorded by Bell (*J.*, 1934, 837) for the reduction product of ethyl *o*-nitrodiphenate. Although this anomalous behaviour has now been observed with the ethyl *o*-nitrodiphenate analogue (V), yet the chemical properties of the reduction product clearly indicated the *lactam* structure (IV;

R = OH). Thus this compound gave a crimson coloration with ferric chloride, a behaviour often associated with an α-hydroxypyridine residue (cf. Köenigs and Geigy, *Ber.*, 1884, **17**, 591). It was insoluble in potassium carbonate solution, but formed bright yellow crystalline salts on treatment with sodium or potassium hydroxide. It failed to give a positive primary amine test on diazotisation followed by coupling with alkaline β-naphthol. Acetylation led to the formation of an unstable *acetyl* derivative (IV; R = OAc), which no longer gave a coloration with ferric chloride and underwent rapid hydrolysis to the original compound on crystallisation from aqueous alcohol (cf. the acetylation of α-hydroxypyridine, Tschitschibabin and Szokow, *Ber.*, 1925, **58**, 2650).

Ethyl 9-*chloro*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene*-4-*carboxylate* (III; R = CO_2Et; R′ = Cl) was readily obtained from the corresponding hydroxy-compound, and passed smoothly into *ethyl* 9-*amino*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene*-4-*carboxylate* (III; R = CO_2Et; R′ = NH_2) on heating with alcoholic ammonia at 200°. The constitution assigned to this compound followed from its reconversion into (III; R = CO_2Et; R′ = OH) by nitrous acid.

Experimental.

M. ps. are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

7-*Nitro*-1 : 3-*dimethyl*-2-*azafluorenone*.—1 : 3-Dimethyl-2-azafluorenone (2 g.) dissolved in concentrated sulphuric acid (10 ml.) was treated at 0° with potassium nitrate (1 g.) added slowly in portions. Reaction was completed by heating on the water-bath for 1 hour; the mixture was then poured on ice and made alkaline with ammonia, and the precipitated product collected and extracted with spirit. The *compound* separated from amyl alcohol in needles, m.p. 230·5° (Found: C, 66·2; H, 4·0; N, 11·0. $C_{14}H_{10}O_3N_2$ requires C, 66·2; H, 4·0; N, 11·0%). Yield, nearly quantitative.

7-*Amino*-1 : 3-*dimethyl*-2-*azafluorenone*.—(*a*) The corresponding nitro-compound (2·1 g.) dissolved in concentrated hydrochloric acid (35 ml.) was treated with stannous chloride (5·5 g.) for 30 minutes on the water-bath. After standing overnight at 0° the product was collected, decomposed with sodium hydroxide, and the precipitated *base* crystallised from spirit (charcoal). If formed brilliant red needles, m. p. 255° (Found: C, 74·3; H, 5·6; N, 12·2. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4; N, 12·5%). The *benzoyl* derivative, bright yellow needles from spirit, m. p. 254° (Found: C, 76·9; H, 5·2; N, 8·8. $C_{21}H_{16}O_2N_2$ requires C, 76·9; H, 4·9; N, 8·5%), was obtained by treating the base (1·1 g.) in pyridine (10 ml.) with benzoyl chloride (900 mg.) for 30 minutes on the water-bath. The *oxime*, orange needles from aqueous pyridine, m. p. 280° (decomp.) (Found: N, 17·3. $C_{14}H_{13}ON_3$ requires N, 17·6%), was obtained by heating the base (4·5 g.), hydroxylamine hydrochloride (4·5 g.), and pyridine (40 ml.) for 30 minutes under reflux, followed by precipitation with ammonia.

(*b*) The amino-derivative [m. p. 255°; prep. by method (*a*)] (4·2 g.) in concentrated hydrochloric acid (50 ml.) was treated with stannous chloride (11 g.) for 1½ hours on the water-bath. After 12 hours at 0° the product was collected and dissolved in water, and sodium hydroxide added in excess. The precipitated 7-amino-1 : 3-dimethyl-2-azafluorenone separated from aqueous spirit as a felted mass of pink needles, m. p. 224—225°, not depressed in admixture with the bright red form, m. p. 255°.

(*c*) The nitro-compound (2 g.) in excess of concentrated hydrochloric acid was reduced with tin (5 g.). After dilution and removal of the tin as sulphide, the filtrate was evaporated to small bulk, and the base precipitated by addition of ammonia. The *product*, which may have been a ?-chloro-7-amino derivative, separated from a large volume of spirit as octahedra, m. p. 303° (Found: C, 63·6; H, 5·9; N, 10·6; Cl, 13·8. $C_{14}H_{11}ON_2Cl$ requires C, 65·0; H, 4·3; N, 10·8; Cl, 13·7%).

Ethyl 5-*Cyano*-4-*phenyl*-2 : 6-*dimethyldihydropyridine*-3-*carboxylate*.—Benzaldehyde (32 g.), β-aminocrotononitrile (25 g.), ethyl β-aminocrotonate (39 g.), and absolute alcohol (50 ml.) were heated under reflux for several days. The solid product was crystallised from aqueous alcohol giving the *ester* in rectangular plates, m. p. 171—172·5° (Found: C, 72·1; H, 6·3; N, 10·0. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9%). Yield, 57 g.

Ethyl 5-*cyano*-4-*phenyl*-2 : 6-*dimethylpyridine*-3-*carboxylate* (I; R = CN; R′ = CO_2Et), large octahedra from light petroleum (b. p. 60—80°), m. p. 101—102° (Found: C, 72·8; H, 5·7; N, 9·8. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%), was obtained by oxidising the above dihydro-ester with four parts of dilute nitric acid (from 1 vol. conc. acid and 7 vols. water) on the water-bath. Yield, 72%.

5-*Cyano*-4-*phenyl*-2 : 6-*dimethylpyridine*-3-*carboxylic Acid* (I; R = CN, R′ = CO_2H).—The above ester (41 g.), potassium hydroxide (9 g.), and absolute alcohol (90 ml.) were heated under reflux for 100 hours. The alcohol was removed on the water-bath, the residue taken up in a little water, and the filtered solution acidified with concentrated sulphuric acid (9 g.) in water. The precipitated acid was crystallised once (charcoal) from aqueous alcohol. The *acid* formed needles, m. p. 236—237° (Found: C, 71·4; H, 4·8; N, 11·1. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). Yield, 27·5 g. (73%).

4-*Carbamyl*-1 : 3-*dimethyl*-2-*azafluorenone* (II; R = CO·NH_2).—A 40% yield was obtained by adhering to the following conditions. The above cyano-acid (20 g.) in concentrated sulphuric acid (80 ml.) was heated in a water-bath for 75 minutes. The *well-cooled* mixture was *slowly* poured with vigorous stirring on a large excess of crushed ice. Ammonia was added in excess and the precipitated *amide* collected and crystallised once (charcoal) from glacial acetic acid. It formed long needles, m. p. 288° (Found: C, 71·2; H, 4·8; N, 10·7. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%).

4-*Amino*-1 : 3-*dimethyl*-2-*azafluorenone* (II; R = NH_2).—Finely powdered 4-carbamyl-1 : 3-dimethyl-2-azafluorenone (20 g.) was added in one portion to a mechanically stirred cooled solution of bromine (15 g.) in 10% potassium hydroxide (250 ml.). The compound rapidly went into solution. After 30 minutes, a further quantity of 10% potassium hydroxide (150 ml.) was added, and the mixture heated on the water-bath for 30 minutes. The product was transferred to an evaporating dish and taken down to dryness on the water-bath. The finely powdered red residual solids were thoroughly extracted with benzene, and the bulked liquors concentrated until crystallisation commenced. The *base* formed squat coral-red needles, m. p. 186·5—187·5° (Found: C, 75·0; H, 5·4; N, 12·3. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4; N, 12·5%). Yield, 50%. The *benzoyl* derivative, faintly yellow silky needles from aqueous methyl alcohol, m. p. 245—246° (Found: C, 76·7; H, 5·0; N, 8·8. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·5%), was prepared by treating the base with benzoyl chloride in pyridine solution at 100°. The *oxime* formed golden-yellow needles from aqueous pyridine, m. p. >300° (Found: N, 17·8. $C_{14}H_{13}ON_3$ requires N, 17·6%).

Ethyl 1 : 3-*Dimethyl*-2-*azafluorenone*-4-*carboxylate* (II; R = CO_2Et).—5-Carbethoxy-4-phenyl-2 : 6-dimethylpyridine-3-carboxylic acid (3·5 g.) (Hantzsch, *loc. cit.*) and concentrated sulphuric acid (7 ml.) were heated on the water-bath for 45 minutes. The cooled mixture was poured on crushed ice and made alkaline with ammonia, and the precipitated *ester* collected and crystallised from aqueous methyl alcohol. It formed silky needles, m. p. 115·5—116·5° (Found: C, 72·4; H, 5·2; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·0%). Alternatively, the silver salt of 1 : 3-di-

methyl-2-azafluorenone-4-carboxylic acid was heated under reflux with excess of ethyl iodide in absolute alcoholic solution for several hours.

Ethyl 9-Hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene 4-carboxylate (III; R = CO_2Et; R′ = OH).—To a solution of ethyl 1 : 3-dimethyl-2-azafluorenone-4-carboxylate (160 g.) in concentrated sulphuric acid (750 ml.) was added, below 10° with mechanical stirring over a period of 4 hours, a solution of sodium azide (68 g.) in water (190 ml.). After a further 4 hours' stirring and cooling, the mixture was left overnight at room temperature. The product was poured on crushed ice and ammonia added in excess. The precipitated sulphate was collected and dissolved in the minimum amount of hot dilute 5% sodium hydroxide solution, and the mixture filtered, cooled, and saturated with carbon dioxide. The precipitated *base* was collected and crystallised three times from spirit. It separated in a felted mass of silky needles, m. p. 255—256° (Found: C, 69·4; H, 5·6; N, 9·7. $C_{17}H_{16}O_3N_2$ requires C, 69·0; H, 5·4; N, 9·5%). Yield, 35%.

Ethyl 9-Chloro-1 : 3-dimethyl-2 : 10-diazaphenanthrene-4-carboxylate (III; R = CO_2Et; R′ = Cl).—The above hydroxy-compound (3 g.), phosphorus pentachloride (2·2 g.), and phosphorus oxychloride (15 ml.) were heated under reflux at 150—160° until all the solid had reacted and gone into solution. Excess of phosphorus halides was removed under reduced pressure on the water-bath, the residue was ground with dilute ammonia, and, after 12 hours at room temperature, the solid was collected. The *product* was extracted once with a little hot spirit and crystallised (charcoal) from benzene–light petroleum. It formed faintly pink octahedra, m. p. 186—187° (Found: Cl, 11·1. $C_{17}H_{15}O_2N_2Cl$ requires Cl, 11·3%). Yield, 55%.

Ethyl 9-Amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene-4-carboxylate (III; R = CO_2Et; R′ = NH_2).—The above chloro-compound (2 g.), saturated alcoholic ammonia (20 ml.), and a trace of copper salt were heated at 180° for 8 hours in a sealed tube. The product was taken to dryness, decomposed by sodium hydroxide solution, and the liberated *base* crystallised once from aqueous acetone and once from benzene–alcohol. It formed flat pale yellow needles, m. p. 200—201° (Found: C, 68·7; H, 5·9; N, 14·1. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·8; N, 14·2%). Yield, 40%. The constitution assigned to this compound followed from its reconversion by nitrous acid in dilute hydrochloric acid into (III; R = CO_2Et; R′ = OH), identified by m. p. and mixed m. p. with an authentic specimen.

Ethyl 9-Hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene-5-carboxylate (IV; R = OH).—Ethyl 4-*o*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (1·5 g.), glacial acetic acid (12·5 ml.), concentrated hydrochloric acid (9 ml.), and stannous chloride (3·25 g.) were heated under reflux for 35 minutes. After 12 hours at 0° the product was collected, dissolved in water (5 ml.), and treated with 10% sodium hydroxide (25 ml.). The yellow sodium salt was collected and dissolved in water (10 ml.), and the *base* liberated by addition of 2N-sulphuric acid (25 ml.). It formed glancing needles, m. p. 184—185° (Found for samples dried in a vacuum at 100° to constant weight: C, 65·7, 65·3; H, 5·3, 5·1; N, 9·2, 9·0. $C_{17}H_{16}O_4N_2$ requires C, 69·0; H, 5·4; N, 9·5%). Yield, 400 mg. On acetylation, an unstable *acetyl* derivative (IV; R = Ac) was obtained, m. p. 171°, which was analysed without purification (Found: C, 65·7; H, 5·2; N, 7·8. $C_{19}H_{18}O_5N_2$ requires C, 67·5; H, 5·3; N, 8·3%). Although this product failed to give a coloration with ferric chloride, recrystallisation from aqueous alcohol led to a substance of indefinite m. p. which gave a crimson coloration. Two crystallisations were sufficient to convert the acetyl derivative back into (IV; R = OH), m. p. 185°.

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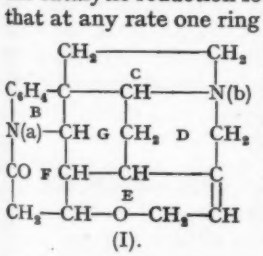
193. *Strychnine. Part II.*

By G. R. CLEMO and R. RAPER.

The catalytic reduction of strychnine with Raney nickel at 220° and 150 atmospheres results in the production of a base, $C_{21}H_{26}O_2N_2$, in which one of the rings is broken, a second base, m. p. 190°, and small quantities of dihydrostrychnine, trimethylamine, and a neutral product.

IN Part I (*J.*, 1936, 1695) certain degradation products of strychnine were described, including 4-methyl-3-ethylpyridine and a bicyclic base, $C_{10}H_{11}N$, whose constitution has not yet been established. Recently further work on strychnine has been carried out and in particular its reduction with hydrogen in the presence of Raney nickel has been examined. In this reaction the main product is a base "D," $C_{21}H_{26}O_2N_2$, of m. p. 252°, and amongst the other products are a trace of dihydrostrychnine, a base "E," m. p. 190°, and small amounts of trimethylamine and a non-basic material which has not yet been identified.

Base "D" gives the usual strychnine colour reactions, and on electrolytic reduction a base $C_{21}H_{28}ON_2$ of the strychnidine type is formed, so that in "D" the $-N(a)-CO-$ system remains intact. The fact that in the catalytic reduction four hydrogen atoms have been added on (two presumably to the double bond) indicates that at any rate one ring has been opened. In "D," N(b) appears to be tertiary as in strychnine—it gives no nitroso-derivative—and since sparteine, which contains *m*-bridged nitrogen ring systems (*J.*, 1933, 644) is unaffected by hydrogenation under the conditions used in this work it is unlikely that either of the rings containing N(b) or ring G has been opened. "D" does not contain an alkoxy-group but gives an acetyl derivative, although the Zerewitinoff determination in xylene is negative (cf. quinol, which gives a negative result in amyl ether, although resorcinol behaves normally. Houben–Weyl, "Methoden der organischen Chemie," 2nd Ed., IV, 793). The electrolytic reduction product of "D," however, gives results agreeing with one hydroxyl group. We infer, therefore, that the 7-membered oxygen containing ring E has been opened to give either a primary or secondary alcohol. If, as we believe, ring "D" is six-membered as it is in the structure now advanced by Robinson (I) (*Experientia*, 1946, II, 38; compare also Prelog and Szpilfogel, *Helv. Chim. Acta*, 1945, **28**, 1669) the production of 4-methyl-3-ethylpyridine is easily explained.



(I).

Further work on the above lines is in progress, but it seems desirable that these results should be recorded at this stage.

EXPERIMENTAL.

Base " D," $C_{21}H_{26}O_2N_2$.—Strychnine (10 g.), methanol (130 c.c.), and Raney nickel (3 g.) were heated and stirred with hydrogen during 4 hours at 100 atm. pressure, the temperature rising to 220° and the pressure to 150 atm. The heating and stirring were continued at these conditions during a further 4 hours * and the autoclave allowed to cool overnight. The resulting methanol solution, which smelled strongly of trimethylamine, was filtered and evaporated (residue A). The distillate of methanol and volatile products was acidified and evaporated to dryness, and the residue basified and extracted with ether. The extract gave, with alcoholic picric acid, a picrate, m. p. 214°, not depressed by admixture with trimethylamine picrate. The colourless solid (residue A) was digested first with warm ether and then with acetone (extracts B and C below), leaving a colourless solid (8·6 g., m.p. 250°) which crystallised from alcohol in well-formed prisms, m. p. 252° (Found: C, 74·3, 74·6: H, 7·7, 7·6; N, 8·5. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7; N, 8·3%). The *substance* gives no precipitate with alcoholic silver nitrate in the micro-Zeisel determination.

Acetyl " D."—When base " D " (0·2 g.) was refluxed during six hours with acetic anhydride (1 c.c.) it was converted into an *acetyl* derivative which crystallised from ethyl acetate in well-formed prisms, m. p. 194° (Found: C, 72·4; H, 7·3; N, 7·4. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4; N, 7·4%). The base was recovered largely unchanged if the heating only lasted one hour, indicating the possibly secondary alcoholic nature of " D."

Electrolytic Reduction of " D."—Base " D " (1·5 g.) in sulphuric acid (50 c.c., 30%) was placed in the cathode compartment of an electrolytic cell (*J.*, 1918, 764) and 5 amps. passed for 16 hours, the temperature being kept below 45° by external cooling. Basification of the cathode liquor gave a solid (1·2 g.) which crystallised from benzene or a little alcohol in colourless prisms, m. p. 217° (Found: C, 77·2; H, 8·6; N, 8·25; active hydrogen, 1·1. $C_{21}H_{28}ON_2$ requires C, 77·8; H, 8·6; N, 8·6%; active hydrogen, 1). We are indebted to Mr. C. G. Moore for the Zerewitinoff determinations. The pink solution of this base in dilute sulphuric acid is changed to intense red on the addition of a trace of chromic acid, whilst an alcoholic solution of the base and *p*-dimethylaminobenzaldehyde acidified with hydrochloric acid becomes dark green on warming.

Ethereal Extract B.—In some experiments this deposited a small amount of material which formed well-defined prisms from acetone, m. p. 219° (Found: C, 74·6; H, 7·05; N, 8·3. Calc. for dihydrostrychnine, $C_{21}H_{24}O_2N_2$: C, 75·0; H, 7·1; N, 8·3%). The major part of the extract (usually 0·8 to 1·1 g.) was a resin from which a *picrate*, stout yellow prisms, m. p. 264° (decomp.), was obtained by adding picric acid in alcohol and recrystallising from glacial acetic acid. The acetone extract C gave the same picrate (Found: C, 52·4; H, 4·7%). The *picrolonate*, m. p. 206°, was crystallised from alcohol (Found: C, 62·0; H, 5·85%). The picrate was not decomposed by cold hydrochloric acid (1 : 1), but, after it had been ground with 2N-sodium hydroxide, ether extracted a *base* which crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 190° [Found: (Weiler and Strauss) C, 76·4, 76·8; H, 7·5, 7·75; N, 8·6, 8·9%. (W. A. Campbell) C, 76·75; H, 7·05%; *M*, 325. It is impossible to deduce any definite formula from these analyses. The hydrogen and nitrogen and molecular weight values, however, all indicate $C_{21}H_{24}ON_2$, which requires C, 78·7; H, 7·5; N, 8·7%; *M*, 320. $C_{21}H_{24}ON_2,C_6H_3O_7N_3$ requires C, 55·0; H, 4·9. $C_{21}H_{24}ON_2,C_{10}H_8O_5N_4$ requires C, 63·7; H, 5·5%]. This difficulty may be due to the presence of an alkyl group on a quaternary carbon atom, as has been occasionally found in the terpene series.

UNIVERSITY OF DURHAM, KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, March 30th*, 1946.]

* In one experiment the temperature accidentally rose to 270° during the second 4-hour period, and the pressure to well over 600 atms. The heating was immediately discontinued to avoid a burst, and after cooling the gases were found to contain 80% of methane, clearly formed by reduction of the methanol.

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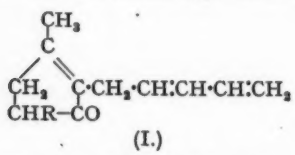
194. *Experiments on the Synthesis of the Pyrethrins. Part II. The Structure of Cinerone.*

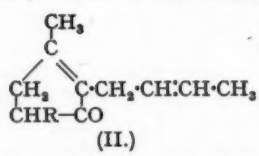
By STANLEY H. HARPER.

During the past year LaForge and Barthel have shown that " pyrethrolone", the keto-alcohol component of the pyrethrins, is a mixture of a C_{11} keto-alcohol, pyrethrolone, and a C_{10} keto-alcohol, cinerolone. In a synthetic approach to the structure of cinerolone and the related ketone, cinerone, a series of 3-*methyl*-2-*butenyl*-Δ^2-cyclo*pentenones* have been prepared. However, neither the expected Δ^β nor the Δ^γ ketones are identical with cinerone. Possible structures for cinerone are considered.

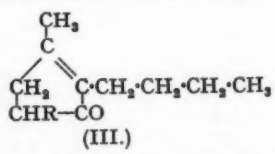
EVIDENCE has been presented during the past year by LaForge and Barthel (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106, 114) that " pyrethrolone," the keto-alcohol component of the pyrethrins, is a mixture. By a combination of fractional distillation and crystallisation of suitable derivatives " pyrethrolone " was separated into the *d*- and *dl*-forms of a keto-alcohol, $C_{11}H_{14}O_2$, and the *d*- and *dl*-forms of a keto-alcohol, $C_{10}H_{14}O_2$. On the basis of analytical data the structure (I, R = OH) was assigned to the C_{11} keto-alcohol and the name pyrethrolone retained. For the C_{10} keto-alcohol structure (II, R = OH) was postulated and the name cinerolone suggested.



(I.)



(II.)



(III.)

LaForge and Barthel found that the molecule of cinerolone was sufficiently stable to enable the hydroxyl group to be replaced by hydrogen, *via* the chloro-compound (II, R = Cl), to give cinerone (II, R = H), which was characterised by a semicarbazone and a *p*-nitrophenylhydrazone.

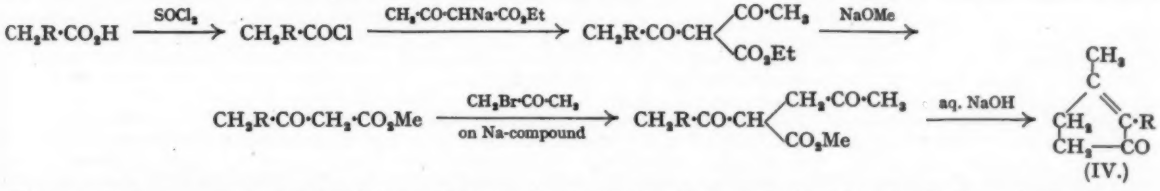
The radical nature of the suggestion that " pyrethrolone " is a mixture not merely of isomers rendered it desirable that this view based on analytical and degradative evidence should be supplemented by a synthetic

approach. Of the two structures that of (II) seemed of the greater interest as being a formula with one carbon atom and one double bond less than previously assigned to " pyrethrolone." In a further paper (*ibid.*, 1945, **10**, 222), received after the work described in this paper had been started, LaForge and Barthel described the reduction of cinerolone to dihydrocinerolone (III, R = OH) and its conversion, *via* the chloro-compound (III, R = Cl), into dihydrocinerone (III, R = H). Derivatives of dihydrocinerone had melting points in moderate agreement with those from synthetic 3-methyl-2-*n*-butyl-Δ^2-*cyclo*pentenone (III, R = H). Their identity was claimed, although apparently no mixed melting points were determined.

Accepting the identity of dihydrocinerone and the *n*-butyl ketone, it follows that in cinerone only the position of the double bond in the side chain is undetermined. LaForge and Barthel assigned this to the Δ^β position on the basis of terminal methyl values. Cinerolone gave 1·66 and its semicarbazone 1·64 terminal methyl groups, apparently indicating the presence of two such groups. It is to be observed, however, that while pyrethrolone, to which structure (I, R = OH) was assigned, gave 1·1 and its semicarbazone 1·1, tetrahydropyrethrolone, with a saturated side chain, gave 1·76 and its semicarbazone 1·85 terminal methyl groups. Reference to Table I will also show that for the synthetic ketones described in this paper there is an equal lack of consistency between terminal methyl content and structure. West, too (*J.*, 1945, 412), has found similar discrepancies in the terminal methyl values for this type of compound. Deductions from terminal methyl values in this series of compounds may therefore be misleading.

If the position of the double bond in cinerone is regarded as not yet settled, there are three possible structures, the Δ^α, Δ^β, and Δ^γ ketones, of which the first two are theoretically capable of existing in *cis*- and *trans*-forms. The Δ^α structure is unlikely, first, because the double bond would be cross conjugated with the $\alpha\beta$-unsaturated carbonyl group, which has been excluded by the examination of the absorption spectrum of " pyrethrolone " (Gillam and West, *J.*, 1942, 671), and secondly, because it would allow of the formation of propaldehyde on ozonisation of " pyrethrolone," which has never been observed (Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 212; LaForge and Haller, *J. Org. Chem.*, 1938, **2**, 546). The Δ^β and Δ^γ structures are equally probable and would be spectroscopically indistinguishable, each showing only the characteristic absorption due to the $\alpha\beta$-unsaturated carbonyl group. LaForge and Barthel report for cinerolone, $\lambda_{max.}$ = 2275 A. (ϵ = 15,500), and for cinerolone semicarbazone, $\lambda_{max.}$ = 2630 A. (ϵ = 22,000), which are consistent with this explanation. These structures could, however, be distinguished unequivocally by ozonisation to give either acetaldehyde or formaldehyde. The separate existence of geometrical isomers in this type of compound has not yet been demonstrated. In the closely analogous case of jasmone (IV, R = Δ^2-pentenyl), despite several syntheses by different routes (Treff and Werner, *Ber.*, 1935, **68**, 640; Hunsdiecker, *ibid.*, 1942, **75**, 460), only one form is known identical with natural jasmone. Moreover the configuration of this is uncertain, being based on that of Δ^3-hexenol, which is itself in dispute (Takei, Ono, and Sinosaki, *ibid.*, 1940, **73**, 950; Stoll and Rouvé, *ibid.*, p. 1358).

As the first step, therefore, in an attempt to clarify this problem by synthesis, a series of 3-*methyl*-2-*butenyl*-Δ^2-cyclo*pentenones* have been prepared by the following method (R = butenyl) from suitable hexenoic acids :



(IV.)

The pure ketones were regenerated from their *semicarbazones* and characterised by physical constants, absorption spectra, and the preparation of derivatives. These and the properties of cinerone recorded by LaForge and Barthel that are comparable are presented in Tables I and II. The Δ^γ structure for cinerone is clearly ruled out by the wide differences in melting points of the comparable derivatives. Likewise the divergences of melting points between the Δ^β ketone and cinerone are such as to make identity improbable. It has been possible, through the courtesy of Dr. LaForge, to test this point by making a direct comparison of the semicarbazones and the *p*-nitrophenylhydrazones of cinerone and the Δ^β ketone; in each case there was a marked depression of melting point. The two substances are therefore different. In view of this unexpected lack of identity, the structure (II, R = H) of the synthetic ketone was placed beyond doubt. The gross structure was confirmed by catalytic reduction of the semicarbazone to the known semicarbazone of 3-methyl-2-*n*-butyl-Δ^2-*cyclo*pentenone (III, R = H) (Hunsdiecker, *Ber.*, 1942, **75**, 455), a specimen of which was prepared for comparison. The position of the double bond in the side chain was confirmed as the Δ^β by the production of acetaldehyde on ozonolysis. The geometrical configuration of the double bond is unknown. During the purification of the ketone no other semicarbazone was isolated. Moreover the starting material, Δ^4-hexenoic acid, is only known in one form of undetermined configuration (Letch and Linstead, *J.*, 1934, 1994). It was then considered that cinerone might be a mixture of the Δ^β and Δ^γ ketones. Several mixtures of the synthetic semicarbazones were made, of which that containing 70% of the Δ^β semicarbazone had the same melting point as cinerone semicarbazone. Nevertheless a mixture gave a well marked depression. Cinerone is therefore different from either ketone singly or in combination.

Despite the absence of positive identification it is considered probable that cinerone is the Δ^β-butenyl

ketone of opposite geometrical configuration to the synthetic ketone described in this paper.* Work is being continued in an attempt to obtain more certain evidence on this point.

TABLE I.

Ketone (IV).	B. p.	$n_D^{25°}$.	$d_4^{25°}$.	$[R_L]_D$* Found.	Calc.	Exaltation.	Terminal methyl values. Found.	Calc.
R = CH_3·CH:CH·CH_3	119°/15 mm.	1·4983	0·9472	46·51	45·26	1·25	1·15	2·00
R = CH_3·CH_2·CH:CH_2	110°/13 mm.	1·4948	0·9407	46·54	45·26	1·28	1·30	1·00
Cinerone	—	1·5067 (29°) 1·4978 (31°)	—	—	—	—	—	—
R = CH_3·CH_2·CH_2·CH_3	105°/10 mm.	1·4794	0·9192	46·99	45·72	1·27	2·00	1·00
Dihydrocinerone	115°/17 mm.	1·4800 (24°)	0·9150 (24°)	47·25	45·72	1·53	—	—

* Using the values C = 2·418, H = 1·100, :O = 2·211, and C:C = 1·733.

TABLE II.

Ketone (IV). M. p.'s of:	Semicarbazone.	*p*-Nitrophenylhydrazone.	2 : 4-Dinitrophenylhydrazone.
R = CH_3·CH:CH·CH_3	220°	162°	161°
R = CH_3·CH_2·CH:CH_2	188	127	146
Cinerone	214—215	148 140—142	—
R = CH_3·CH_2·CH_2·CH_3	193	133	155
Dihydrocinerone	191·5—192·5 (corr.)	128—131 (corr.)	149—151 (corr.)

EXPERIMENTAL.

(Melting points are uncorrected. Microanalyses, including terminal methyl values by the micro Kuhn–Roth procedure, are by Drs. Weiler and Strauss, Oxford.)

Δ^3-Hexenoic acid was prepared from *n*-butaldehyde and malonic acid (Boxer and Linstead, *J.*, 1931, 748; Linstead and Noble, *J.*, 1933, 559) and purified by low temperature crystallisation. Δ^3-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 50°/17 mm. and 54°/20 mm. Δ^4-Hexenoic acid was prepared from crotyl chloride and ethyl malonate (Eccott and Linstead, *J.*, 1929, 2163). Δ^4-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 58°/20 mm. Δ^5-Hexenoic acid was prepared from Δ^3-butenyl bromide and ethyl malonate (Linstead and Rydon, *J.*, 1934, 1998; Michael and Mason, *J. Amer. Chem. Soc.*, 1943, **65**, 684). Δ^5-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 50°/15 mm. *n*-Hexoyl chloride, prepared using thionyl chloride, had b. p. 54°/20 mm.

The following generalised procedures were used:

Ethyl α-Hexenoylacetoacetates.—Ethyl acetoacetate (71·5 g.; 0·55 mol.) was added in portions to sodium wire (12·7 g.; 0·55 atom) under dry ether (500 c.c.). Gentle refluxing was maintained for 4 hours to complete the formation of the sodio-compound. The mixture was then cooled and the hexenoyl chloride (66·3 g.; 0·5 mol.) added in small portions with shaking to moderate the violent reaction. Reaction was completed by refluxing for 30 minutes. Ice-water, acidified with sulphuric acid, was added, and the ethereal layer was separated, washed, and dried (Na_2SO_4). Removal of the ether and fractional distillation of the residue gave the required ester. The Δ^4-*hexenoyl* ester (65% yield) had b. p. 143°/15 mm. (Found: C, 63·6; H, 8·2. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%); the Δ^5-*hexenoyl* ester (60% yield) had b. p. 148°/16 mm. (Found: C, 64·1; H, 7·75%); the *n*-hexoyl ester (79% yield) had b. p. 145°/15 mm. Each ester gave a deep red colour with alcoholic ferric chloride. The product from Δ^3-hexenoyl chloride tended to decompose on distillation (b. p. 140—155°/20 mm.) and the bright yellow distillate was heterogeneous. This could be overcome by using a higher vacuum; the product then had b. p. 100—110°/0·5 mm. (41% yield) (Found: C, 64·5; H, 7·8%). This ester gave only a pale red colour with alcoholic ferric chloride.

Methyl γ-Butenylacetoacetates.—The ethyl α-hexenoylacetoacetate (113 g.; 0·5 mol.) was added to a cold solution of sodium (12·5 g.; 0·55 atom) in methanol (250 c.c.). After 24 hours, water and dilute sulphuric acid were added, and the esters extracted with ether. The ethereal extract was washed and dried (Na_2SO_4), and the ether removed. Fractional distillation of the residue gave, after a forerun of methyl hexenoate, the required methyl γ-butenylacetoacetate. The Δ^2-*butenyl* ester (65% yield) had b. p. 118°/15 mm. (Found: C, 63·3; H, 8·6. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%); the Δ^3-*butenyl* ester (71% yield) had b. p. 125°/23 mm. (Found: C, 63·8; H, 8·3%); the *n*-butyl ester (64% yield) had b. p. 114°/15 mm. and 120°/20 mm. Each ester gave a deep purple red colour with alcoholic ferric chloride. The Δ^3-hexenoyl condensation product failed to give a fraction corresponding to methyl γ-Δ^1-butenylacetoacetate. Apart from a low boiling fraction of methyl hexenoate and methyl acetoacetate, the remaining material had a b. p. similar to that of the original condensation product (135—155°/17 mm.; 100—105°/0·3 mm.) and like it gave only a pale red colour with alcoholic ferric chloride (Found: C, 66·1; H, 7·1. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). It seems probable that under the conditions employed the original condensation has proceeded abnormally, at least in part, with the elimination of C_2H_6O (alcohol?) from the expected hexenoylacetoacetate, to give a *product* that does not suffer alcoholysis with sodium methoxide. This condensation is being studied in the hope of making the Δ^α-butenyl ketone available by this route.

Methyl α-Hexenoyl-lævulates.—The methyl γ-butenylacetoacetate (42·5 g.; 0·25 mol.) was added in portions to sodium wire (6·3 g.; 0·27 atom) under dry ether (250 c.c.). The sodio-compound was moderately soluble in ether thus facilitating reaction of the sodium. After being refluxed for 1 hour the mixture was cooled, and freshly distilled bromoacetone (34 g.; 0·25 mol.) (*Org. Synth.*, Coll. Vol. **2**, 88) added in small portions with shaking; a transient bright pink colour being formed initially. Reaction was completed by refluxing for 30 minutes. Ice-water, acidified with sulphuric acid, was added, and the ethereal layer was separated, washed, and dried (Na_2SO_4). The ether was distilled off and low-boiling fractions removed by a water pump at 100°. The residual condensation product was used directly for cyclisation. Attempted distillation of part of the Δ^4-hexenoyl ester led to partial decomposition (b. p. 165—170°/20 mm.) and the distillate was discoloured.

3-*Methyl*-2-*butenyl*-Δ^2-cyclo*pentenone*.—The crude methyl α-hexenoyl-lævulate (56·5 g.) was stirred at 70° (thermometer in flask) with 3% aqueous sodium hydroxide (800 c.c.) for 3 hours. The solution was cooled and acidified with

* This is consistent with the results of the ozonisation of cinerolone (Dr. LaForge, private communication to the author).

sulphuric acid, and the liberated ketone extracted with ether (4 × 100 c.c.). The ethereal extract was washed and dried (Na_2SO_4), and the ether taken off through a column. The residue was distilled and the crude cyclic ketone (24 g.) collected as a fraction, b. p. 110—130°/20 mm. The crude ketone was converted into the semicarbazone by using the pyridine–ethanol method (Haller and LaForge, *J. Org. Chem.*, **1936**, **1**, 38) and the sparingly soluble product recrystallised from methanol, ethanol, or ethyl acetate. The *Δ$^{\beta}$-butenyl semicarbazone* had m. p. 220° (decomp.), $\lambda_{max.}$ = 2660 A. (ϵ = 21,800) in alcohol (Found: C, 63·7; H, 8·4; N, 20·2. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3; N, 20·2%); the *Δ$^{\gamma}$-butenyl semicarbazone* had m. p. 188° (decomp.) (Found: C, 63·5; H, 8·3%); the *n*-butyl semicarbazone had m. p. 193°.

Regeneration of Ketones.—The pure semicarbazone (5·0 g.) was added to a solution of oxalic acid (10 g.) in water (50 c.c.) and the suspension heated under reflux on the steam-bath for 1 hour in a stream of nitrogen. After cooling, the separated ketone was taken up in light petroleum (25 c.c.) and the extract dried (Na_2SO_4). After removal of the solvent through a column the residue was distilled from a small Claisen flask and the pure ketone collected as one fraction of constant b. p. (3·1 g.) (see Table I). Portions were immediately sealed for analysis and the physical constants (see Table I) determined without delay. All these ketones on analysis showed low carbon contents, owing presumably to the slow absorption of atmospheric oxygen. A similar phenomenon has been observed for pyrethrolone (LaForge and Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1779) and cinerolone (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 118). The *Δ$^{\beta}$-butenyl ketone* [Found (after 1 week): C, 78·9; H, 9·45; (after 3 weeks): C, 77·1; H, 9·5. $C_{10}H_{14}O$ requires C, 80·0; H, 9·4%] had $\lambda_{max.}$ = 2350 A. (ϵ = 12,000) in alcohol. A portion left for 5 months in contact with air "dried" to a viscous resin, no longer soluble in light petroleum. The *Δ$^{\gamma}$-butenyl ketone* (Found: C, 79·5; H, 9·25%) and *n*-butyl ketone (Found: C, 77·8; H, 10·95. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%) had the constants shown.

Using the freshly regenerated ketones, the following derivatives were prepared by standard methods:

The *Δ$^{\beta}$-butenyl p-nitrophenylhydrazone*, red prisms from methanol, m. p. 162° (Found: C, 67·2; H, 6·8; N, 14·9. $C_{16}H_{19}O_2N_3$ requires C, 67·35; H, 6·7; N, 14·7%); *2 : 4-dinitrophenylhydrazone*, crimson needles from ethanol, m. p. 161° (Found: C, 58·2; H, 5·6; N, 16·9. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 16·9%); *oxime*, plates from light petroleum, m. p. 123° (Found: C, 72·4; H, 9·0; N, 8·4. $C_{10}H_{15}ON$ requires C, 72·6; H, 9·1; N, 8·5%). The *Δ$^{\gamma}$-butenyl p-nitrophenylhydrazone*, red prisms from aqueous methanol, m. p. 127° (Found: C, 67·1; H, 6·9; N, 14·6%); *2 : 4-dinitrophenylhydrazone*, crimson needles from ethanol, m. p. 146° (Found: C, 58·5; H, 5·7; N, 16·6%). The *n*-butyl *p*-nitrophenylhydrazone, light red prisms from methanol, m. p. 133°; 2 : 4-dinitrophenylhydrazone, crimson needles from ethanol, m. p. 155°. The 2 : 4-dinitrophenylhydrazones were superior to the *p*-nitrophenylhydrazones for the purposes of characterisation, being obtained in much higher yield and being more readily crystallised.

Ozonisation of Ketones.—(1) The *Δ$^{\beta}$*-butenyl ketone (500 mg.) in carbon tetrachloride (25 c.c.) was ozonised at 0° (30 minutes), the exit gases being passed through a solution of dimedone (1·2 g.) in water (300 c.c.). After completion of the ozonisation, water (25 c.c.) was added to the ozonide and aspiration continued for 24 hours, the volatile products from the decomposition of the ozonide being led through the dimedone. The dimedone derivative of acetaldehyde (298 mg.; 29% yield) was collected, dried at 90°, and had m. p. 140·5° (not depressed by admixture with an authentic specimen). There was no sign of the production of formaldehyde.

(2) Experiment (1) was repeated using as the absorbing solution 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid. Acetaldehyde 2 : 4-dinitrophenylhydrazone (240 mg.; 32% yield) was collected, and after crystallisation from ethanol had m. p. 168° (not depressed by admixture with an authentic specimen).

(3) The *Δ$^{\gamma}$*-butenyl ketone (500 mg.) was ozonised as in (1), using dimedone as the absorbing solution. The dimedone derivative of formaldehyde (273 mg.; 28% yield) was collected and after crystallisation from aqueous ethanol had m. p. 190° (not depressed by admixture with an authentic specimen). There was no sign of the production of acetaldehyde.

Hydrogenation.—The *Δ$^{\beta}$*-butenyl ketone semicarbazone (258 mg.) was added to previously reduced Adams's catalyst (50 mg.) in ethyl acetate (40 c.c.). The suspension was hydrogenated, absorption being slow owing to the sparing solubility. Hydrogen equivalent to one double bond was taken up in 3 hours. The product dissolved on boiling and after filtering from the catalyst separated as shining flakes on cooling (203 mg.), m. p. 193° alone or mixed with an authentic specimen of the *n*-butyl ketone semicarbazone.

Mixed Melting Points with Derivatives of Cinerone.—(1) A mixture of approximately equal parts of cinerone and *Δ$^{\beta}$*-butenyl ketone semicarbazones, after being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 210°. At the same time cinerone semicarbazone went brown at 190°, softened at 200°, and melted with decomposition at 213°.

(2) A mixture of approximately equal parts of the *p*-nitrophenylhydrazones of cinerone and the *Δ$^{\beta}$*-butenyl ketone melted on being put in the bath at 140° (m. p. 135—140°). At the same time cinerone *p*-nitrophenylhydrazone had m. p. 148—150°.

(3) The *Δ$^{\beta}$*- (39·5 mg.) and the *Δ$^{\gamma}$*-butenyl ketone semicarbazone (16·7 mg.) were mixed and crystallised from ethanol (5 c.c.). The product, on being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 215°. This mixture (12·5 mg.) and cinerone semicarbazone (12·5 mg.) were crystallised together from ethanol (2 c.c.). This mixed product, on being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 202°.

The author is indebted to Dr. A. E. Gillam for the spectroscopic determinations, to Dr. F. B. LaForge for the specimens of cinerone derivatives, and to Mr. J. D. Thompson for assistance in the preparation of *Δ^{3}*-butenol. He is grateful for grants from the Chemical Society and Imperial Chemical Industries, Ltd., which have covered the costs of chemicals and microanalyses respectively.

UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, February 21st*, 1946.]

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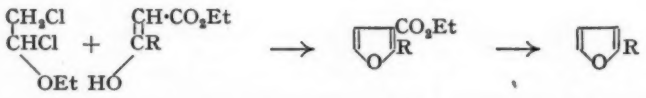
195. *Synthesis of 2-Arylfurans.*

By A. W. JOHNSON.

Interaction of furan with aryldiazonium chlorides in the presence of alkali, or with nitrosoacetanilides, yields 2-arylfurans with minor quantities of 3-arylfurans. By these methods the following have been prepared; 2-phenyl-, 2- and 3-p-*chlorophenyl*-, 2-p-*nitrophenyl*-, 2-m-*chlorophenyl*-, 2-p-*bromophenyl*-, and 2-α-*naphthyl-furan*. The structure of 2-*p*-chlorophenylfuran has been rigidly proved by independent synthesis and by the nature of the Diels–Alder adduct with acetylenedicarboxylic ester. Light-absorption data clearly differentiate between 2- and 3-arylfurans.

2-ARYLFURANS have been prepared previously in small quantities by the two following laborious routes :

(i) The condensation of 1 : 2-dichlorodiethyl ether with aroylacetic esters in the presence of 10% ammonium hydroxide yields a mixture of the 2-arylfuran-3-carboxylic ester together with the pyrrole analogue which is separated by fractionation. Hydrolysis and decarboxylation of the 2-arylfuran-3-carboxylic ester gives the corresponding 2-arylfuran :



The method is based on that of Benary (*Ber.*, 1911, **44**, 493) who synthesised 2-methylfuran from ethyl acetoacetate. 2-Phenylfuran (Kondo and Suzuki, *J. Pharm. Soc. Japan*, 1927, **544**, 501; Fujita, *ibid.*, 1925, **519**, 450) and 2-*p*-chlorophenylfuran (Wibaut and Dhont, *Rec. Trav. chim.*, 1943, **62**, 272) have been synthesised by this method.

(ii) 4-Benzoyl-2-phenylfuran, obtained by a complicated synthesis, was converted into 2-phenylfuran-4-carboxylic acid by a Beckmann rearrangement of the oxime and hydrolysis of the amide. Decarboxylation of the acid gave 2-phenylfuran (Fuson, Fleming, and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1994). No chemical reactions of the 2-arylfurans have been described.

Other aryl substituted heterocyclic compounds have been prepared by the normal methods for the union of aryl nuclei (Bachmann and Hoffman, " Organic Reactions," 1944, **2**, 224), *e.g.*, arylthiophens (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339), arylpyrroles (Rinkes, *Rec. Trav. chim.*, 1943, **62**, 116), and arylpyridines (Heilbron, Hey, *et al.*, *J.*, 1940, 349, 355, 358, 372, 1279; 1943, 441). Of these methods the so-called Gomberg reaction is the most common : $ArN_2OH + Ar'H \longrightarrow Ar{\cdot}Ar' + N_2 + H_2O$. It is known that furan readily couples with aryldiazonium chlorides (Gilman, Wooley, and Vanderwal, *Proc. Iowa Acad. Sci.*, 1932, **29**, 176; Ochiai, *J. Pharm. Soc. Japan*, 1938, **58**, 1025), but the possibility of formation of arylfurans by the reaction of furan with alkaline or neutral solutions of diazonium hydroxides has not been investigated previously.

A modification of the Gomberg reaction as described by Elks, Haworth, and Hey (*J.*, 1940, 1284) was used for the condensation in which the equivalent quantity of aqueous sodium hydroxide or sodium acetate was added to a well-stirred mixture of the aqueous diazonium chloride and furan at 5—10°. In all the cases examined, the main identified product was the 2-arylfuran. The reaction between *p*-chlorobenzenediazonium acetate and furan has been examined in detail, and 3-p-*chlorophenylfuran* has been isolated in 0·7% yield as compared with the 29% yield of 2-*p*-chlorophenylfuran. In addition, traces of a higher-melting product were isolated from the reaction but the structure of this has not been determined.

The following 2-arylfurans have also been obtained by this method : 2-phenylfuran (22%), 2-p-*nitrophenylfuran* (20%), 2-m-*chlorophenylfuran* (16%), 2-p-*bromophenylfuran* (15%), 2-α-*naphthylfuran* (18%) (and its *picrate*). 2-*p*-Aminophenylfuran (isolated as its *phenylurea*) was obtained from 2-*p*-nitrophenylfuran by hydrogenation at room temperature and pressure in the presence of Raney nickel.

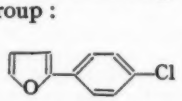
Other standard methods of effecting the union of aryl nuclei have been investigated, in particular the reaction of furan with *p*-chloronitrosoacetanilide [obtained according to equation (i) and employed as shown in equation (ii)] (Heilbron, Hey, *et al.*, *J.*, 1940, 369, 372). This method has already been used for the preparation of arylpyridines (Heilbron, Hey, *et al.*, *locc. cit.*) and arylpyrroles (Rinkes, *loc. cit.*). 2-*p*-Chlorophenylfuran, identical with the product obtained by the Gomberg method, was obtained from the reaction in 19% yield :

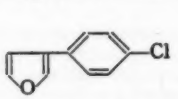
(i) $RNH{\cdot}CO{\cdot}CH_3 + NOCl + KOAc \longrightarrow RN(NO){\cdot}CO{\cdot}CH_3 + KCl + HOAc$

(ii) $RN(NO){\cdot}CO{\cdot}CH_3 +$ $\longrightarrow$ $R + N_2 + CH_3{\cdot}CO_2H$ ($R = p\text{-}Cl{\cdot}C_6H_4$)

An attempt to condense 1-*p*-chlorophenyl-3 : 3-dimethyltriazen with furan in the presence of hydrogen chloride or acetic acid (I.G., B.P., 513,846; Elks and Hey, *J.*, 1943, 441) was unsuccessful.

The arylfurans rapidly darkened on standing in air at room temperature and were best preserved in dark bottles. The physical constants of the phenylfuran obtained as the main identified product from the Gomberg reaction agreed closely with the values for 2-phenylfuran given in the literature (Kondo and Suzuki, *loc. cit.*; Fuson, Fleming, and Johnson, *loc. cit.*) but as phenylfuran was a liquid it was decided to study the orientation of the aryl groups of the readily obtainable solid *p*-chlorophenylfurans, the m. p. of the main product (74—75°) being appreciably higher than that given (67°) by Wibaut and Dhont (*loc. cit.*) for 2-*p*-chlorophenylfuran. It is evident that if the *p*-chlorophenyl group is in the 2-position of the furan nucleus, it is conjugated with both of the double bonds of the furan ring, but if it is in the 3-position then only the Δ^2-double bond is in conjugation with the aryl group :





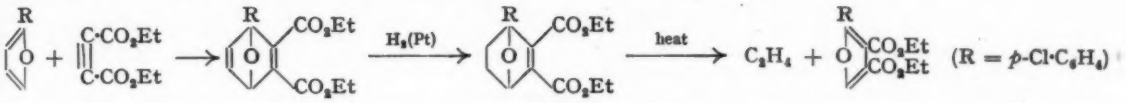
A determination of the ultra-violet absorption spectra of the two isomers in chloroform solution showed that the higher-melting product was the 2-*p*-chlorophenyl isomer and that the lower-melting product was the

3-*p*-chlorophenyl isomer. The ultra-violet absorption spectra of styrene and 1-phenylbutadiene are given for comparison (Dimroth, *Z. angew. Chem.*, 1939, **52**, 545).

	Maximum (A.).	$\epsilon_{max.}$
Isomer, m. p. 74—75°	2870	20,600
$PhCH{:}CH{\cdot}CH{:}CH_2$	2800	24,400
Isomer, m. p. 50—51°	2620	13,200
$PhCH{:}CH_2$	2450	15,000

The positions of the maxima of the ultra-violet absorption curves are at a greater wave-length for the *p*-chlorophenylfurans than for the corresponding phenylethylenic hydrocarbons as the double bonds conjugated with the *p*-chlorophenyl group are themselves part of a cyclic system. The chlorine atom has a negligible effect on the absorption spectrum over the wave-lengths under consideration. The presence of a phenyl group in conjugation is roughly equivalent to 1·5 conjugated double bonds (Dimroth, *loc. cit.*).

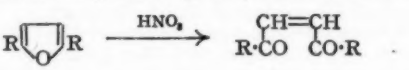
A further proof that the product, m. p. 74—75°, from the Gomberg reaction of furan and *p*-chlorobenzenediazonium acetate was 2-*p*-chlorophenylfuran was afforded by the Diels–Alder addition to ethyl acetylenedicarboxylate (cf. Alder and Rickert, *Ber.*, 1937, **70**, 1354; Hofmann, *J. Amer. Chem. Soc.*, 1944, **66**, 51, 157; 1945, **67**, 421). The primary addition product (I) was hydrogenated in the presence of Adams's catalyst, when the dihydro-adduct (II) was obtained, which on heating lost ethylene and gave *ethyl* 2-p-*chlorophenylfuran*-3 : 4-*dicarboxylate*, m. p. 60—61°. Had the *p*-chlorophenyl group been in the 3-position in the furan ring, *p*-chlorostyrene would have been eliminated with the formation of furan-3 : 4-dicarboxylic ester :



(I.) (II.)

2-*p*-Chlorophenylfuran has been synthesised by a method essentially that of Wibaut and Dhont (*loc. cit.*), and the product proved to be identical with the main product isolated from the reaction of furan with *p*-chlorobenzenediazonium acetate or *p*-chloronitrosoacetanilide. The 1 : 2-dichlorodiethyl ether required for the synthesis was obtained by the addition of chlorine to ethyl vinyl ether in chloroform solution. An attempted condensation of the more readily available 1 : 2-*dichloroethyl* isobutyl *ether* with ethyl *p*-chlorobenzoylacetate was unsuccessful.

Lutz and Wilder (*J. Amer. Chem. Soc.*, 1934, **56**, 978) have described the oxidation of 2 : 5-diarylfurans to 1 : 2-diaroylethylenes, usually in excellent yields, by the action of nitric acid in acetic acid :



All attempts to convert 2-*p*-chlorophenylfuran into β-*p*-chlorobenzoylacrylic acid by this method have been unsuccessful, and *p*-chlorobenzoic acid was obtained in every experiment.

Experimental.

Preparation of Arylfurans.—The amine (½ mole) in presence of concentrated hydrochloric acid (160 c.c.) and water (90 c.c.) was diazotised in the normal manner with aqueous sodium nitrite. The filtered diazonium solution was added to furan and vigorously stirred at 5—10° while a solution of 5N-sodium hydroxide (300 c.c.) (method *A*) or a solution of sodium acetate (160 g. of trihydrate) in water (400 c.c.) (method *B*) was added over ½ hour. Stirring was continued for 48 hours, the reaction being allowed to continue at room temperature after the first 5 hours. The furan layer was then separated, washed with water, and dried. After removal of the excess of furan the residue was purified by distillation under reduced pressure or in steam.

Phenylfuran.—Prepared by method *A*. The crude product (25·7 g.) was distilled in a vacuum and the following fractions obtained: (i) 3·0 g., b. p. 70—80°/15 mm., $n_D^{20°}$ 1·5547; (ii) 16·3 g., b. p. 92—95°/10 mm., $n_D^{20°}$ 1·5920. Fraction (ii) was 2-phenylfuran (22%) (Fuson, Fleming, and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1994, give b. p. 107—108°/18 mm., $n_D^{20°}$ 1·5968, for 2-phenylfuran). Fraction (i) has not been further investigated.

p-*Chlorophenylfuran.*—Prepared by method *A*. The crude product was distilled in steam (3 hours) and the first 200 c.c. of the distillate kept separate from the remainder. The oil which was obtained in the main distillate rapidly solidified and was separated (25 g.; 29%) and crystallised from aqueous methanol when 2-*p*-chlorophenylfuran was obtained as colourless plates, m. p. 74—75° (Found: C, 67·3; H, 4·2; Cl, 19·6. Calc. for $C_{10}H_7OCl$: C, 67·2; H, 3·9; Cl, 19·9%). 2-*p*-Chlorophenylfuran slowly darkens in air and gives a permanganate-coloured solution in concentrated sulphuric acid from which the original furan is not precipitated on dilution.

The oil which was obtained in the first portion of the steam distillation was extracted with ether (3 × 100 c.c.); the combined ethereal extracts were dried and the solvent was removed. After three days at room temperature the residual oil (2·5 g.) partly solidified and the solid (approx. 1 g.; m. p. 67—69°) separated; this, after crystallisation from aqueous methanol, had m. p. 74—75° alone and in admixture with authentic 2-*p*-chlorophenylfuran. The filtrate was distilled in a vacuum and the main fraction, b. p. 95—115°/10 mm. (0·6 g.), collected. On cooling, the distillate solidified; it had m. p. 50—51° after repeated crystallisations from light petroleum (b. p. 60—80°) (mixed m. p. with 2-*p*-chlorophenylfuran, 38—45°) (Found: C, 67·1; H, 3·8. $C_{10}H_7OCl$ requires C, 67·2; H, 3·9%). The product, 3-p-*chlorophenylfuran*, dissolved in concentrated sulphuric acid to give an orange coloured solution.

The residue from the steam distillation was extracted with benzene (3 × 150 c.c.); the combined benzene extracts were washed and the solvent was removed. The residue was sublimed in a vacuum at 100°; 2-*p*-chlorophenylfuran (1 g.) was first obtained, followed by an unidentified compound (0·1 g.) which formed colourless needles, m. p. 86—87°, from light petroleum (b. p. 40—60°).

2-p-*Nitrophenylfuran*.—Prepared by method *B*. The crude product was dissolved in benzene (100 c.c.) and purified by chromatography on alumina. The bright yellow band was eluted with benzene containing 5% of methanol, leaving a dark brown residue, and the solvent was removed from the eluate. The residual *product* formed yellow needles after crystallisation from aqueous ethanol, m. p. 134—135° (19·0 g.; 19·7%) (Found: C, 63·25; H, 3·45; N, 7·4. $C_{10}H_7O_3N$ requires C, 63·4; H, 3·7; N, 7·4%).

2-m-*Chlorophenylfuran*.—Prepared by method *A*. The crude product was distilled in steam (3 hours) and the distillate extracted with ether (3 × 250 c.c.). The combined ethereal extracts were washed with 2N-sodium hydroxide and then water, and dried. The residue after removal of solvent was distilled in a vacuum; 2-m-*chlorophenylfuran* was thus obtained as a colourless oil (14 g.; 16%), b. p. 137°/15 mm.; $n_D^{25°}$ 1·6053 (Found: C, 66·9; H, 4·2; Cl, 19·7. $C_{10}H_7OCl$ requires C, 67·2; H, 3·9; Cl, 19·9%).

2-p-*Bromophenylfuran*.—Prepared by method *A* on 0·1-mole scale. The crude product was distilled in steam. The yellow solid obtained in the distillate was separated and crystallised from aqueous methanol to yield 2-p-*bromophenylfuran* (3·35 g.; 15%) as colourless plates, m. p. 85—86° (Found: C, 54·1; H, 3·4; Br, 35·8. $C_{10}H_7OBr$ requires C, 53·8; H, 3·1; Br, 35·9%).

2-α-*Naphthylfuran*.—Prepared by method *B*. The residue was distilled in steam (4 hours) and the distillate extracted with ether (3 × 200 c.c.), and the combined ethereal extracts were washed with 2N-sodium hydroxide and water, and dried. After removal of the solvent the residue was distilled in a vacuum. The main fraction, 2-α-*naphthylfuran*, was a pale yellow oil (17·3 g.; 18%), b. p. 90—91°/0·02 mm. (Found: C, 86·5; H, 5·0. $C_{14}H_{10}O$ requires C, 86·6; H, 5·2%). The *picrate*, m. p. 105—106°, formed dark red prisms from methanol (Found: C, 56·65; H, 3·0; N, 10·2. $C_{20}H_{13}O_8N_3$ requires C, 56·7; H, 3·1; N, 9·9%). A little naphthalene was obtained as a white sublimate in the condenser in the early stage of the distillation.

2-p-*Aminophenylfuran*.—A suspension of 2-*p*-nitrophenylfuran (1 g.) in methanol (70 c.c.) was hydrogenated at room temperature and pressure in the presence of Raney nickel (1 g.). The absorption of hydrogen was very rapid, and three equivalents (456 c.c. at N.T.P. Calc. for $C_{10}H_7O_3N \longrightarrow C_{10}H_9ON$, 462 c.c.) were absorbed after 14 minutes, when absorption ceased. The catalyst was separated and the solvent removed leaving 2-*p*-aminophenylfuran as a pale yellow solid, m. p. 53—54° after crystallisation from light petroleum (b. p. 40—60°). The solid decomposed to a brown oil when kept in air for 2 days, and owing to this fairly rapid decomposition a satisfactory analysis was not obtained. The corresponding *phenylurea*, m. p. 227—228°, formed colourless plates from ethanol (Found: C, 73·5; H, 5·3; N, 10·15. $C_{17}H_{14}O_2N_2$ requires C, 73·2; H, 5·1; N, 10·1%).

Reaction of p-*Chloronitrosoacetanilide with Furan*.—A mixture of *p*-chloroacetanilide (18 g.), acetic anhydride (80 c.c.), acetic acid (80 c.c.), fused potassium acetate (12 g.), and phosphoric oxide (1 g.) was stirred and cooled to 8°, while a stream of nitrosyl chloride was passed in until excess was present (brown fumes emitted). The mixture was poured into ice-water (1000 c.c.) and the precipitated *p*-chloronitrosoacetanilide rapidly separated and dried on a porous tile. The solid was dissolved in furan (500 c.c.), and the solution dried (Na_2SO_4) and left overnight. Nitrogen was evolved from the solution. The excess of furan was removed on the steam-bath and the residue distilled in steam. 2-*p*-Chlorophenylfuran was obtained in the distillate as a pale brown solid which was separated and crystallised from aqueous methanol. The product (3·65 g.; 19%) formed colourless plates, m. p. 74—75° alone and mixed with the product of the Gomberg reaction.

1-p-*Chlorophenyl*-3 : 5-*dimethyltriazen*.—An aqueous solution of diazotised *p*-chloroaniline (½ mole) was added slowly from a cooled dropping funnel to a cooled stirred mixture of dimethylamine (25%; 100 g.) and sodium carbonate (130 g.) in water (400 c.c.). Stirring was continued for ½ hour and the precipitated 1-p-*chlorophenyl*-3 : 3-*dimethyltriazen* separated, washed, pressed, and crystallised from aqueous methanol; it formed colourless plates, m. p. 56—57° (78 g.; 85%) (Found: N, 22·5; Cl, 19·3. $C_8H_{10}N_3Cl$ requires N, 22·9; Cl, 19·3%).

Reaction of 1-p-*Chlorophenyl*-3 : 3-*dimethyltriazen with Furan*.—1-*p*-Chlorophenyl-3 : 3-dimethyltriazen (20 g.) was dissolved in a mixture of furan (200 c.c.) and acetic acid (30 c.c.) and the solution heated under reflux overnight. The excess of furan was removed on the steam-bath and the black tarry residue extracted with ether (3 × 100 c.c.), and the combined ethereal extracts were washed and dried, and the solvent was removed. The residue was a dark coloured oil which could not be induced to crystallise.

Repetition of the above experiment using excess of dry hydrogen chloride instead of acetic acid also failed to yield any *p*-chlorophenylfuran.

1 : 2-*Dichlorodiethyl Ether*.—A solution of chlorine (18 g.) in carbon tetrachloride (200 c.c.) was added slowly to a solution of ethyl vinyl ether (20 g.) in carbon tetrachloride (50 c.c.) with stirring and ice cooling. The mixture was stirred overnight and the solvent then removed on the steam-bath. The residue was distilled in a vacuum, and 1 : 2-dichlorodiethyl ether was obtained as a colourless oil (18 g.; 45%), b. p. 43—45°/15 mm. [Wildman and Gray (*J. Amer. Chem. Soc.*, 1919, **41**, 1122) give b. p. 66—69°/45 mm.]. There was a considerable black residue after the distillation.

Condensation of 1 : 2-*Dichlorodiethyl Ether and Ethyl* p-*Chlorobenzoylacetate*.—Ethyl *p*-chlorobenzoylacetate, m. p. 37—38° [Thorp and Brunskill (*J. Amer. Chem. Soc.*, 1915, **37**, 1261) give m. p. 38°], was prepared in 45% yield by the condensation of ethyl *p*-chlorobenzoate and ethyl acetoacetate according to the method of McElvain and Weber (*Org. Synth.*, 1943, **23**, 35).

The condensation of ethyl *p*-chlorobenzoylacetate and 1 : 2-dichlorodiethyl ether was effected in the presence of 10% ammonia solution, the method and extraction being essentially that described by Wibaut and Dhont (*Rec. Trav. chim.*, 1943, **62**, 272). The ethyl 2-*p*-chlorophenylfuran-3-carboxylate, b. p. 125—130°/0·1 mm., was not purified but the crude product was hydrolysed to the corresponding acid, m. p. 193—194° (from light petroleum, b. p. 80—100°) [Wibaut and Dhont (*loc. cit.*) give m. p. 194°]. 2-*p*-Chlorophenylfuran-3-carboxylic acid (0·2 g.) was heated in a sealed tube at 275° overnight. The product was extracted with ether (3 × 20 c.c.); the combined ethereal extracts were washed with sodium hydrogen carbonate solution and dried, and the solvent was removed. The residue was crystallised from aqueous methanol with carbon clarification and yielded 2-*p*-chlorophenylfuran (0·08 g.), m. p. 70—71° alone and on admixture with the product of the Gomberg reaction. Lack of material prevented the complete purification of this product.

1 : 2-*Dichloroethyl* iso*Butyl Ether*.—A solution of chlorine (15 g.) in carbon tetrachloride (150 c.c.) was added to a solution of *iso*butyl vinyl ether (20 g.) in carbon tetrachloride (20 c.c.) at 0° with stirring. The addition was very rapid and, after 15 minutes' stirring, the solvent was removed on the steam-bath and the residue distilled in a vacuum to yield 1 : 2-*dichloroethyl* iso*butyl ether* (30·2 g.) as a colourless oil, b. p. 85°/43 mm., 82°/37 mm., $n_D^{21°}$ 1·642 (Found: Cl, 41·4. $C_6H_{12}OCl_2$ requires Cl, 41·5%).

Reaction of 2-p-*Chlorophenylfuran and Ethyl Acetylenedicarboxylate*.—2-*p*-Chlorophenylfuran (9·6 g.) and ethyl acetylenedicarboxylate (9·1 g.) were heated at 100° overnight. The crude product was dissolved in ethyl acetate (70 c.c.) and hydrogenated over Adams's platinum catalyst (0·5 g.) at room temperature and pressure. Absorption of hydrogen had almost ceased after 5½ hours when approximately ⅞ of the theoretical volume of hydrogen for one equivalent (1200 c.c.) had been taken up. The reaction was then discontinued, the catalyst separated, and the residue distilled

in a vacuum. The main fraction, b. p. 168—170°/0·2 mm. (5·9 g.), solidified on cooling and after crystallisation from light petroleum (b. p. 60—80°) had m. p. 60—61°; it was *ethyl* 2-p-*chlorophenylfuran*-3 : 4-*dicarboxylate* (Found: C, 59·1; H, 4·45; Cl, 11·3. $C_{16}H_{15}O_5Cl$ requires C, 59·5; H, 4·65; Cl, 11·0%).

The author is indebted to Mr. J. D. Rose for advice throughout the work, and to Dr. A. Lambert who made the original suggestion that 2-arylfurans might be obtained by the methods described.

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196. *The Vapour Pressure of Phthalic Anhydride.*

By D. A. CROOKS and (MISS) F. M. FEETHAM.

The vapour pressure of phthalic anhydride has been measured over the temperature range 30—143°. The latent heat of fusion calculated from the results has been checked by direct calorimetry. The results are compared with published data.

IN the course of work requiring a knowledge of the vapour pressure of solid phthalic anhydride at temperatures below 60°, various anomalies were discovered in the available data for the vapour pressure of solid and liquid phthalic anhydride.

Unpublished German data are quoted (Landolt–Börnstein, " Tabellen," Erg. IIb, 1309) for the vapour pressure of solid phthalic anhydride in the temperature range 20—130°. The latent heat of sublimation at the m. p., calculated from these data by the Clapeyron–Clausius equation, is 96·5 cals./g. Two sets of measurements of the vapour pressure of liquid phthalic anhydride have been published. From measurements by Monroe (*J. Ind. Eng. Chem.*, 1919, **11**, 1116; 1920, **12**, 969), the calculated latent heat of vaporisation of liquid phthalic anhydride at the m. p. is 87·3 cals./g. From earlier measurements by Ramsay and Young (*Phil. Trans.*, 1886, *A*, **177**, 103) the latent heat of vaporisation is calculated to be 100·4 cals./g., which exceeds the calculated heat of sublimation. The difference between the heat of sublimation and the heat of vaporisation calculated from Monroe's data is only 9·2 cals./g., whereas Monroe calculates the heat of fusion to be 37·02 cals./g. from the cryoscopic constant.

Further discrepancies are found between the vapour pressures of the solid and liquid phthalic anhydride obtained by extrapolating the above data to the m. p. In view of these differences, the vapour pressure of phthalic anhydride was measured at temperatures from 30° to 143°, and the latent heat of fusion was checked by direct calorimetry.

Two methods were used to measure the vapour pressure. From 30° to 60°, the indirect method of Menzies (*J. Amer. Chem. Soc.*, 1920, **42**, 2218) was used; from 90° to 143° the vapour pressure was large enough to be measured directly on a mercury manometer.

The vapour pressures so determined can be related to the absolute temperature T by the following equations:

$$\text{For solid phthalic anhydride, } \log_{10}P = 12{\cdot}249 \pm 0{\cdot}005 - (4632 \pm 18)/T.$$

$$\text{For liquid phthalic anhydride, } \log_{10}P = 9{\cdot}209 \pm 0{\cdot}002 - (3410 \pm 44)/T.$$

Hence, from the Clapeyron–Clausius equation, the latent heat of sublimation is calculated to be $143{\cdot}0_5 \pm 0{\cdot}5_6$ cals./g., and the latent heat of vaporisation to be $105{\cdot}3_1 \pm 1{\cdot}3_6$ cals./g., giving by difference $37{\cdot}7_4 \pm 1{\cdot}4_7$ cals./g. for the latent heat of fusion. Direct calorimetric measurement gave 37·5 ± 0·8 cals./g. for the latter, in good agreement with Monroe's indirect determination from the cryoscopic constant and with the value calculated from the vapour-pressure measurements reported below.

The four sets of results are compared in the figure.

EXPERIMENTAL.

The sample of phthalic anhydride used had been purified by repeated sublimation; m. p. 130·2°.

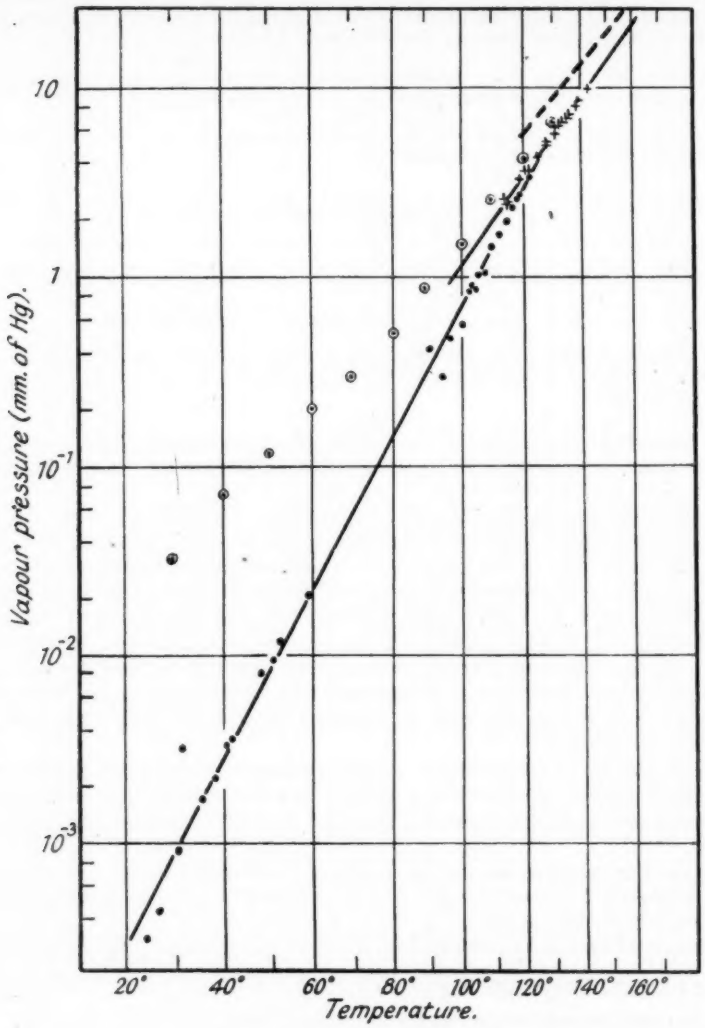
Vapour-pressure Determinations.—(a) For temperatures between 30° and 60°, Menzies's method was used, in which the vapour displaces permanent gas from a vessel of known volume at the temperature at which the vapour pressure is to be measured into another volume, including a McLeod gauge, at a constant temperature. The vapour is prevented from diffusing from one vessel to the other by a cold trap. Then if v is the volume of the vessel containing vapour at pressure P and gas at pressure $(P_1 - P)$ at temperature T, and if V is the volume of the second vessel containing only gas at pressure P_1 and temperature T_R, then

$$P = (P_1 - P_0)VT/vT_R + P_1 - P_0T/T_0$$

where P_0 is the pressure of gas in the apparatus at some temperature T_0, low enough for the vapour pressure to be negligible.

The results of measurements with phthalic anhydride are given in Table I. The ratio of volumes in the apparatus used was 0·480 and T_R was constant throughout at 290° K. In the final column of Table I, the values of $\log_{10}P$ calculated from the equation $\log_{10}P = 12{\cdot}249 - 4632/T$ are given (P in mm. of mercury) for comparison with the observed values.

(b) For temperatures between 90° and 145°, the vapour pressure was measured directly on a mercury manometer completely immersed in a thermostat so that the vapour pressure of mercury and the effects of surface tension were



——— *Present measurements.*
○○ *Data from Landolt and Börnstein's tables.*
– – – *Extrapolated from data by Monroe.*

TABLE I.

Vapour pressure of solid phthalic anhydride.

T, ° K.	10^3P_1.	$10^3(P_1 - P_0)\frac{TV}{T_BV}$.	$10^3P_0\frac{T}{T_0}$.	10^3P.	$\log_{10}P$.	$\log_{10}P_{(calc.)}$.
264·0	$54{\cdot}2_9$	—	—	—	—	—
303·3	$60{\cdot}2_8$	$3{\cdot}0_1$	$62{\cdot}3_6$	$0{\cdot}9_3$	$\bar{4}{\cdot}968$	$\bar{4}{\cdot}977$
313·6	$63{\cdot}2_0$	$4{\cdot}6_2$	$64{\cdot}4_8$	$3{\cdot}3_4$	$\bar{3}{\cdot}524$	$\bar{3}{\cdot}479$
248·1	$52{\cdot}3_2$	—	—	—	—	—
274·7	$56{\cdot}3_8$	$1{\cdot}8_6$	$57{\cdot}9_3$	$0{\cdot}3_1$	$\bar{4}{\cdot}491$	$\bar{5}{\cdot}387$
299·7	$59{\cdot}9_0$	$3{\cdot}7_6$	$63{\cdot}2_1$	$0{\cdot}4_5$	$\bar{4}{\cdot}643$	$\bar{4}{\cdot}794$
308·3	$61{\cdot}9_1$	$4{\cdot}8_6$	$65{\cdot}0_2$	$1{\cdot}7_5$	$\bar{3}{\cdot}243$	$\bar{3}{\cdot}225$
314·6	$63{\cdot}8_2$	$6{\cdot}1_0$	$66{\cdot}3_5$	$3{\cdot}5_7$	$\bar{3}{\cdot}553$	$\bar{3}{\cdot}526$
323·6	$68{\cdot}8_9$	$8{\cdot}8_8$	$68{\cdot}2_5$	$9{\cdot}5_2$	$\bar{3}{\cdot}979$	$\bar{3}{\cdot}936$
260·9	$72{\cdot}3_8$	—	—	—	—	—
304·6	$80{\cdot}6_4$	$4{\cdot}1_6$	$84{\cdot}5_0$	$0{\cdot}3_0$	$\bar{4}{\cdot}477$	$\bar{3}{\cdot}042$
311·0	$83{\cdot}0_4$	$5{\cdot}4_8$	$86{\cdot}2_8$	$2{\cdot}2_4$	$\bar{3}{\cdot}350$	$\bar{3}{\cdot}355$
320·9	$88{\cdot}4_9$	$8{\cdot}5_6$	$89{\cdot}0_2$	$8{\cdot}0_2$	$\bar{3}{\cdot}904$	$\bar{3}{\cdot}815$
325·6	$91{\cdot}6_9$	$10{\cdot}4_1$	$90{\cdot}3_3$	$11{\cdot}7_7$	$\bar{2}{\cdot}071$	$\bar{2}{\cdot}023$
332·1	$98{\cdot}4_2$	$14{\cdot}3_1$	$92{\cdot}1_3$	$20{\cdot}6_0$	$\bar{2}{\cdot}314$	$\bar{2}{\cdot}301$

identical in both limbs. The results of three series of measurements are given in Table II in the order in which they were made. On reducing the temperature below the m. p., super-cooling occurred down to about 114°.

TABLE II.

Vapour pressure of phthalic anhydride.

Temp.	*P.*	State.	Temp.	*P.*	State.	Temp.	*P.*	State.
135·1°	6·99	Liquid	103·6°	0·90	Solid	103·6°	0·87	Solid
128·4	5·16	Supercooled	111·9	1·72	,,	116·2	2·38	,,
121·1	3·62	,,	118·5	2·71	,,	91·1	0·42	,,
115·2	2·55	,,	130·9	6·13	Liquid	109·3	1·46	,,
104·0	0·82	Solid	135·5	7·27	,,	117·9	2·63	,,
95·0	0·30	,,	143·2	9·88	,,	132·4	6·37	Liquid
			138·4	8·03	,,	139·6	8·53	,,
			133·6	6·51	,,	130·7	5·69	,,
			128·1	5·01	Supercooled	124·9	4·30	Supercooled
			121·8	3·61	,,	119·2	3·29	,,
			114·7	2·44	,,	114·1	2·63	,,
			107·7	1·05	Solid	105·8	1·02	Solid
			100·6	0·56	,,	97·5	0·48	,,
						114·8	2·00	,,
						122·1	3·39	,,

Latent Heat of Fusion.—The latent heat of fusion was measured directly in order to check the value calculated from the vapour pressures. About 10 g. of phthalic anhydride, sealed into a glass tube, were warmed to a known temperature and then rapidly plunged into a calorimeter containing about 180 g. of water. The resulting rise in temperature was measured on a mercury thermometer and suitable cooling corrections were made. In this way, the latent heat of fusion and the specific heat of liquid and solid phthalic anhydride were determined. Three determinations of the latent heat of fusion gave 36·9, 38·4, and 37·2 cals./g. severally.

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197. *The Estimation of Sulphur Trioxide in its Mixtures with Sulphur Dioxide by the Method of Amperometric Titration.*

By D. W. E. AXFORD and T. M. SUGDEN.

The method of amperometric titration has been used to determine the sulphur trioxide content of sulphur dioxide–sulphur trioxide mixtures in which the proportion of the latter is about 2% of the whole. The gases were absorbed in N-sodium hydroxide, followed by acidification and removal of sulphur dioxide by a current of nitrogen, with glycerol in the solution to inhibit oxidation of the sulphite. The sulphate solution was then neutralised and titrated amperometrically with lead nitrate solution using a simple type of polarograph.

IN the course of investigations on the oxidation of sulphur dioxide in flue gases, it was necessary to develop a method of estimation of the sulphur trioxide in a system which contained a large excess of the dioxide (SO_2/SO_3 of the order 50 : 1). The dioxide in such a mixture may readily be determined by iodometric titration, but the determination of the trioxide presents considerable difficulties.

The only available alternative to the usual gravimetric methods is due to Taylor and Johnstone (*J. Ind. Eng. Chem. Anal.*, 1929, **1**, 197), depending on the filtration of the trioxide mist through a fine-grain alundum crucible. Another method, utilising the principle of amperometric titration, after absorption of the gases in sodium hydroxide, is described below and has been found to give good results.

Although a sulphur trioxide mist is difficult to absorb in water, it has been found possible to obtain complete dissolution of it by bubbling the gases through N-sodium hydroxide.

EXPERIMENTAL.

Determination of Sulphate by Amperometric Titration.—A full description of this mode of use of the polarograph is given in " Polarography " (Kolthoff and Lingane, Inter-Science Pub. Inc., 1941).

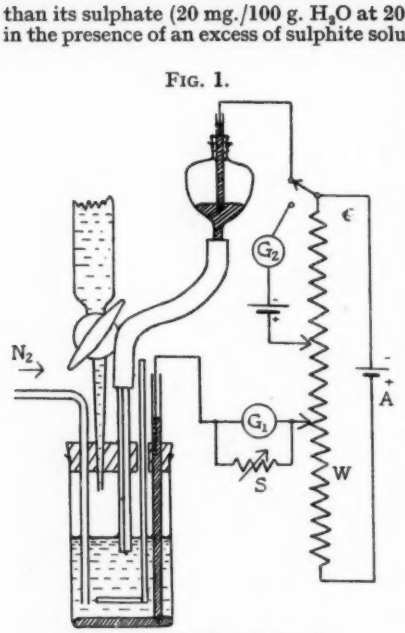
A. *Apparatus.*—A simple form of polarograph was employed (see Fig. 1). The cell was a glass beaker of about 100 c.c. capacity with a shallow pool of mercury as anode, and the dropping-mercury electrode consisted of a piece of carefully cleansed thermometer tubing, the rate of fall being adjusted to give one drop in about three seconds. The top of the cell was closed by a rubber stopper through which passed the capillary tube, the tip of the burette, the inlet tube for a stream of inert gas, and a hole for a glass stirrer. The potential applied to the cell was obtained from a potentiometer box *P*, connected to a 2-volt accumulator *A*, with the cell in series with the galvanometer G_1, shunted by a variable resistance *S*. The potentiometer box was standardised by a Weston cell *W*, and the applied potential to the cell measured by the setting of the box. The galvanometer G_1 was a Cambridge moving-coil instrument with lamp and scale, and a sensitivity of about 1 cm. scale division per microamp. It was used to obtain the current through the cell, with the shunt *S* at a suitable value. The absolute value of the current need not be known, since relative changes only are required.

B. *Choice of Precipitant.*—Two suitable cations were available : barium (solubility of sulphate, 0·24 mg./100 g. H_2O at 20°; half-wave potential in neutral solution, −1·95 volts) and lead (solubility of sulphate, 4·1 mg./100 g. H_2O at 20°; half-wave potential in neutral solution, −0·41 volt).

(1) *Use of barium.* Of these two, barium appeared the more suitable since its sulphite is considerably more soluble

than its sulphate (20 mg./100 g. H_2O at 20°), and it was considered that this might permit of the titration of the sulphate in the presence of an excess of sulphite solution, whereas the possibility does not exist with lead, which has a very insoluble sulphite. Estimations of sulphate with barium by this method have already been performed by Heyrovský and Berezický (*Coll. Czech. Chem. Comm.*, 1929, **1**, 19) and by Majer (*Z. Elektrochem.*, 1936, **42**, 120). It was unsuitable, however, in the present work for the following reasons. First, the half-wave potential of barium lies close to those of sodium and potassium, the hydroxides of which in fairly concentrated solution would be necessary for the absorption of the gases, and it was difficult to separate their diffusion currents from that of barium; and secondly, direct titrations of *N*/100-barium chloride gave end-points which were too high by 10—20%, which was considered to be due to the absorption of barium chloride on the precipitated sulphate. It was therefore decided to use lead.

FIG. 1.



Polarograph cell and circuit.

(2) *Use of lead.* The use of lead nitrate as a precipitant for sulphate demands the removal of the sulphite because of its high insolubility. It has been used as an amperometric reagent for sulphate by Majer (*loc. cit.*) and by Kolthoff and Pan (*J. Amer. Chem. Soc.*, 1940, **62**, 3332), and has been found to be satisfactory under the conditions used in the present work, as follows: (i) The titration is carried out in presence of ethyl alcohol, as recommended by Spalenka (*Coll. Czech. Chem. Comm.*, 1939, **11**, 146), to reduce the solubility of lead sulphate. (ii) Addition of solid lead sulphate to prevent supersaturation. (iii) Addition of a small quantity of methyl-orange to suppress polarographic current maxima. (iv) Potassium salts may not be used as ground electrolytes since low end-points are obtained owing to precipitation of a double potassium lead sulphate. Hence in the absorption of the gases it was necessary to use sodium hydroxide.

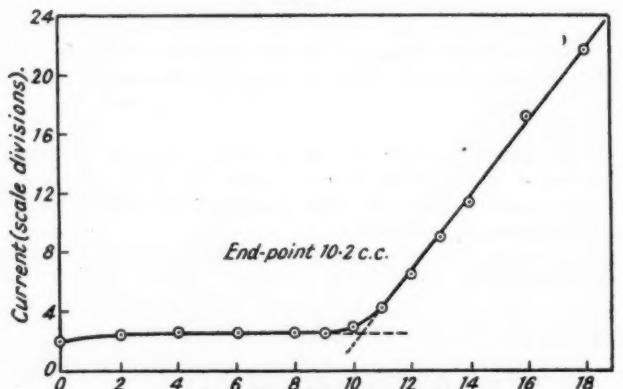
A typical result is shown in Fig. 2. The titrations were carried out in an atmosphere of nitrogen, and the potential of the cathode was set at −0·8 volt, *i.e.*, well above the half-wave potential of lead in neutral or acid solution. The accuracy with solutions of concentrations of the order of N/100 was within about 2%.

It was found sufficient to use a large pool of mercury as anode (area about 12 sq. cm.) since, according to Majer (*loc. cit.*), if the current density is small, it is practically unpolarised, even in nitrate and sulphate solutions. Since Kolthoff and Pan (*J. Amer. Chem. Soc.*, 1939, **61**, 3402) note that a slight polarisation of the anode does not affect the results of amperometric titrations, it was found more convenient to use this very simple form of anode rather than the standard calomel electrode required when an accurate knowledge of the potential of the cathode is desired. All the solutions used were made up with distilled water which had been freed from dissolved air and carbon dioxide by boiling.

Procedure for Sulphate–Sulphite Solutions.—A series of experiments using solutions of known sulphate content was next undertaken. If the original dioxide and trioxide are absorbed in N-sodium hydroxide a typical resulting solution would be represented by: NaOH(~N), Na_2SO_4(~N/200), Na_2SO_3(~N/10). Test solutions of this order of concentration were made by using sulphate in known amount and passing sulphur dioxide into the solution from a syphon. The solution was acidified with N-nitric acid. A few drops of glycerol were added to the alkali in the first place to inhibit oxidation of sulphite in solution. The dioxide was then blown out by passing a stream of nitrogen for 30 minutes, and the solution then rendered just alkaline to methyl-orange by addition of N-sodium hydroxide, and titrated with N/100-lead nitrate as previously.

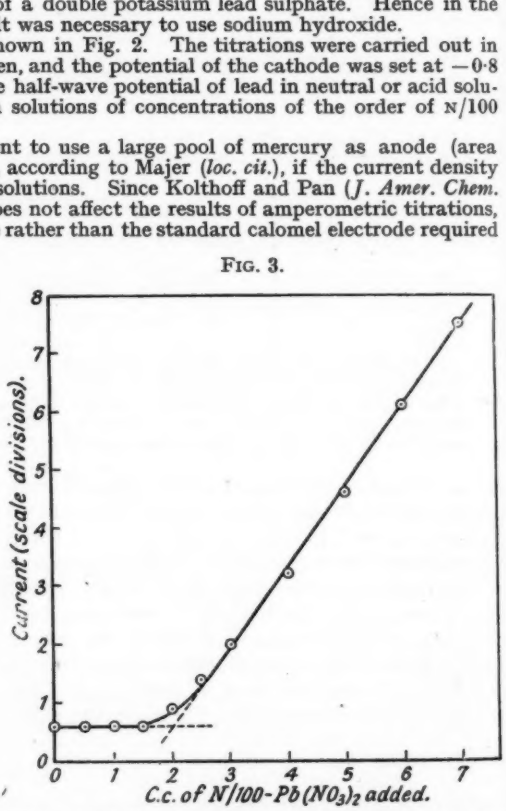
A convenient check on the complete removal of dioxide was available since this substance in acid solution gives a

FIG. 2.



5 *c.c.* N/50-H_2SO_4 + 5 *c.c.* N-NaOH *neutralised with* N-HNO_3 *(methyl-orange indicator)* + 5 *c.c. ethyl alcohol* + *solid lead sulphate. Cathode potential* — 0·8 *volt. Nitrogen passed for* 2 *mins. after each addition of* $Pb(NO_3)_2$.

FIG. 3.



5 *C.c. of solution* A + 10 *c.c.* N-HNO_3 + 5 *c.c. ethyl alcohol. Nitogen passed for* 45 *mins.* N-NaOH *added until just alkaline to methyl-orange. Titrated with* N/100-$Pb(NO_3)_2$ *solution. Cathode potential* −0·8 *volt. Nitrogen blown for* 2 *mins. after each addition of* $Pb(NO_3)_2$.

diffusion current at $-0{\cdot}3$ volt. The absence of such a current at the P.D. used for the titration ($v_1 = -0{\cdot}8$ volt = applied potential) was taken to indicate complete removal. The solution was arranged to be about neutral since lead hydroxide (solubility = 15·5 mg./100 g. H_2O at 20°) is liable to be precipitated in alkaline solution, and since at the potential employed an appreciable hydrogen-ion concentration might have yielded a sufficient diffusion current to interfere with the titration.

The end-points corresponded to the original sulphate concentration with an accuracy of within 2%, thus showing that the glycerol added effectively inhibited the oxidation of sulphite in the solution.

Comparison with Gravimetric Estimation of Sulphate.—A final test of the amperometric method was obtained by analysing a sulphate–sulphite solution of unknown sulphate concentration both amperometrically and gravimetrically. Sulphur dioxide from a gas-burette was passed through a vertical Pyrex tube containing pure concentrated sulphuric acid kept at about 280° by means of an external heating coil. Arrangement was made for the passage of the same specimen of dioxide through the hot acid several times in order to pick up sufficient sulphuric acid. The resulting mixture of gases was absorbed in a further gas-burette containing a known volume of N-sodium hydroxide with a little glycerol and methyl-orange present. The solution was divided into two portions A and B.

Analysis of A. A polarographic estimation as previously described was performed after removal of the dioxide from the solution by a stream of nitrogen (see Fig. 3).

Analysis of B. The solution was acidified with hydrochloric acid and the dioxide blown out by a stream of nitrogen for an hour. A solution of N/5-barium chloride was then added dropwise to the boiling solution until the precipitation was complete. The barium sulphate was filtered off, washed, and dried in the usual way.

Results.	Amperometric.	Gravimetric.
Normality of sulphate solution	0·0057	0·0059
	0·0040	0·0038

The accuracy of these results justifies the application of the method to the determination of the trioxide in presence of the dioxide, provided suitable absorption can be obtained. An amperometric titration can be performed in about an hour, which represents a considerable saving of time on the gravimetric method.

Procedure for Gaseous Mixtures.—N-Sodium hydroxide has been found to be a suitable absorbent which does not interfere with the later polarographic analysis. The absorption was carried out by bubbling the gas at a known rate through the alkali in a specially constructed wash-bottle containing 10 c.c. of solution with glycerol and methyl-orange, and fitted with a burette tap at the base for withdrawal. The height of the liquid column was about 8 cm.

A test of the efficiency of this arrangement was made by running two of them in series. There was never any detectable sulphate in the second bottle whereas the order of concentration in the first was N/200-sulphate. The smallest concentration detectable by this method was about N/5000, so the first wash-bottle appeared to have effectively absorbed the trioxide. The solution from the wash-bottle was run out directly into the polarograph cell containing excess of N-nitric acid, and removal of the dioxide commenced at once by blowing nitrogen through. Hence the solution was never exposed for an appreciable time to the air. Titration, as above, was carried out with N/50-lead nitrate.

We are grateful to Professor R. G. W. Norrish, F.R.S., and Dr. F. S. Dainton for useful discussions in the course of this work.

PHYSICAL CHEMISTRY LABORATORY, CAMBRIDGE. [*Received, February 21st,* 1946.]

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198. *Strychnine and Brucine. Part XLII. Constitution of the* neo-*Series of Bases and their Oxidation Products.*

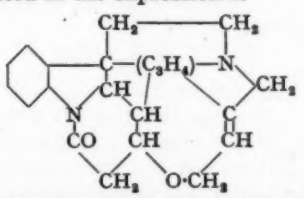
By L. H. BRIGGS, H. T. OPENSHAW, and SIR ROBERT ROBINSON.

An alternative strychnine (brucine and colubrine) formula is feasible in which N(b) is joined to position 4 of the tetrahydrocarbazole nucleus, instead of to position 3 as hitherto postulated. An advantage is gained in that the new possible structure contains a β-collidine skeleton in addition to those of carbazole and tryptamine. In addition a biogenetic relation to cinchonine can be perceived.

The obstacles to consideration of this modification of the formulæ were the formation and properties of methoxymethyl*chano*dihydrostrychnone and these have not yet been removed by a reinterpretation of the chemistry of the *neo*-series of bases.

The action of *p*-nitrobenzenediazonium chloride on *neo*strychnine and methoxymethyldihydro*neo*strychnine results in the formation of derivatives that are devoid of basic properties. They are undoubtedly *p*-nitrophenylhydrazones of keto-amides containing ·N(b)·CO·. The consequences are discussed and it is concluded that a change of view in regard to the skeleton of the alkaloids could only be entertained after acceptance of one of two alternative theories of the structure of the oxidation products of the *neo*-bases. It is now found that the reduction of methyl*neo*strychnidinium chloride by means of sodium amalgam does not afford methyl*chano*dihydro*neo*strychnidine *des*-base-A, m. p. 143°, but instead methyldihydrostrychnidinium-A chloride. The *des*-base-A, m. p. 143°, is therefore, in all probability, methyl*chano*dihydrostrychnidine. The constitutions of the series of Hofmann elimination products on this basis are indicated.

UNAMBIGUOUS experimental proofs are now available covering the whole periphery of the strychnine molecule and what is certainly known * is formulated in the expression I.



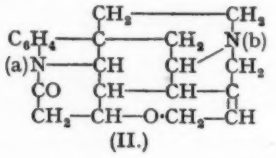
(I.)

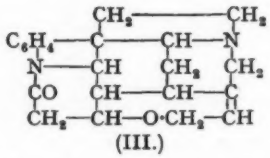
* The hydrogen atom shown attached to the α-position of the indole nucleus is included because evidence has been obtained that one of the so-called " colourless " benzylidene derivatives is a benzyl-α-pyridone. This work will shortly be submitted for publication.

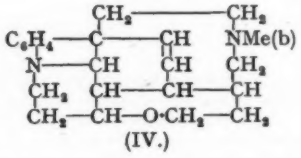
It is also known that strychnine contains :N(b)—CH<C/C because ψ-strychnine (hydroxystrychnine) (Warnat, *Helv. Chim. Acta*, 1931, **14**, 997; Blount and Robinson, *J.*, 1932, 2305; 1934, 595; Leuchs, *Ber.*, 1937, **70**, 1543 and later papers) is a tertiary alcohol. If in addition to this condition, we also exclude 4-rings there remain eight structures most conveniently symbolised after noting that quadrivalent C_3H_4 is (a)·CH_2·CH(b)·CH:(c, c) or (α, α):CH·CH_2·CH:(β, β); the possibilities ·CH_2·CH_2·C: and ·CH_2–$\dot{C}$–CH_2· could not give ·N(b)·CH:. The eight structures are therefore :

C(a) (b)N / C (A) C / C(c) (c)C — C(c) (b)N / C (B) C / C(a) (c)C — C(c) (c)N / C (C) C / C(a) (b)C — C(c) (c)N / C (D) C / C(b) (a)C — C(a) (c)N / C (E) C / C(c) (b)C — C(b) (c)N / C (F) C / C(c) (a)C — C(α) (α)N / C (G) C / C(β) (β)C — C(β) (α)N / C (H) C / C(α) (β)C

(A) written in full is II, the constitution hitherto preferred, and (G) is III which we consider a good alternative. The other six structures offer no advantages and can be discussed along lines analogous to those of the sequel. The cyclic ether ring is seven-membered in (A) and (G), eight-membered in (C), (D), and (E) and nine-membered in (B), (F), and (H).


(II.)


(III.)


(IV.)

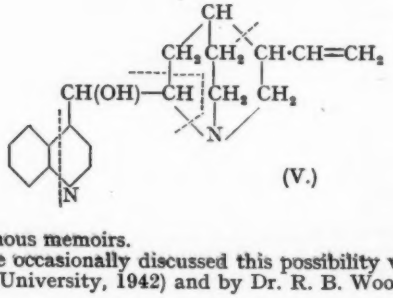
It may be noted that the *des*-base-D (Achmatowicz and Robinson, *J.*, 1934, 581) must on either basis have the structure IV.

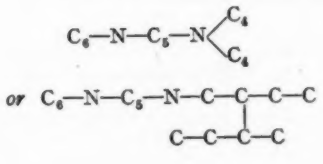
This *des*-base, on catalytic reduction in acid solution furnishes no dihydro-base but a methyldihydrostrychnidinium-D salt and a much smaller proportion of a methyldihydrostrychnidinium-A salt, by a kind of reversed Emde process. When a model of IV is constructed it is found that N(b) lies almost equidistant from the two carbon atoms of the double bond, and structures based on II and III are made with equal ease on the model and are both strainless. This fact led to a discussion as long ago as 1936 of the correctness of the assignment of the structure type-II to the A-series and type-III to the D-series. A transposed allocation was an obvious possibility and was seen to possess advantages.

The idea was, however, abandoned on account of our inability to explain the formation and properties of methoxymethyl*chano*dihydrostrychnone on the basis of III for strychnine.

Reference to earlier memoirs (Clemo, Perkin, and Robinson, *J.*, 1927, 1589; Gulland, Perkin, and Robinson, *ibid.*, p. 1627; Perkin and Robinson, *J.*, 1929, 964; Achmatowicz, Perkin,* and Robinson, *J.*, 1932, 486; Achmatowicz, Clemo, Perkin,* and Robinson, *ibid.*, p. 775; Perkin,* Robinson, and Smith, *ibid.*, p. 1239; *idem*, *J.*, 1934, 574; Achmatowicz and Robinson, *ibid.*, p. 581; Briggs and Robinson, *ibid.*, p. 590; Reynolds and Robinson, *ibid.*, p. 592; Robinson, *ibid.*, p. 1490; Reynolds and Robinson, *J.*, 1935, 935; Achmatowicz and Robinson, *ibid.*, p. 1291; Achmatowicz, Lewi, and Robinson, *ibid.*, p. 1685; Achmatowicz, *J.*, 1938, 1472) may be made for an account of these matters and it will be appreciated that the difficulty was a very real one. Our further studies have narrowed the structural possibilities in the *neo*-series but have not made the acceptance of III easier. This matter is discussed in the sequel. On certain other grounds III† has notable advantages which may be mentioned in explanation of our interest in this alternative. Alkaline degradation of strychnine or certain derivatives (*e.g.*, methylstrychnine, strychninolone) furnishes various substances among which indole, 3-ethylindole, tryptamine, carbazole, β-collidine (4-methyl-3-ethylpyridine), and a base $C_{10}H_{11}N$ (Clemo) have been recognised (Kotake, *Proc. Imp. Acad. Tokyo*, 1936, **12**, 99; Kotake, Mori, and Mitsuwa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 129; Clemo, *J.*, 1936, 1695; Clemo and Metcalfe, *J.*, 1937, 1518). The formula III contains the β-collidine skeleton but II requires a migration before it can provide it.

We are impressed by the fact that III exhibits a close structural relation to cinchonine, the molecule of which (V) may be dissected into units, in general agreement with an early theory (Robinson, *J.*, 1917, **111**, 876), as illustrated.

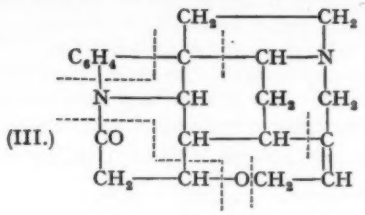

(V.)



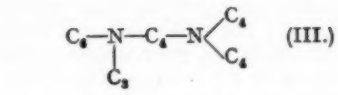
* Posthumous memoirs.

† We have occasionally discussed this possibility with other chemists. It was raised at a meeting of the Alembic Club (Oxford University, 1942) and by Dr. R. B. Woodward of Harvard University in the summer of 1945.

The dissection of III is similar :

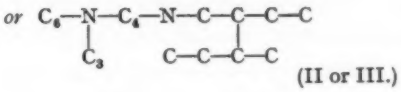


(III.)



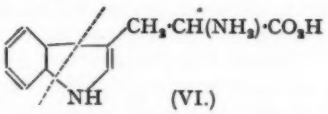
(III.)

or

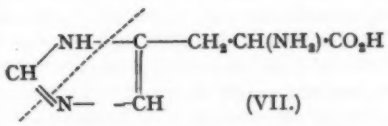


(II or III.)

Thus in cinchonine we have a lysine progenitor (*proto*lysine) and in strychnine a *proto*-ornithine, *plus* a triose. In this connexion it should be recalled that we have already recognised a *proto*-ornithine progenitor in tryptophan (VI) and histidine (VII) as well as in the solanaceous alkaloids. These hypotheses apply only to phytochemical syntheses, not to bacterial metabolisms.



(VI.)



(VII.)

The enlargement of a pyrrolidine to a pyridine ring is conceivable in an alkaline degradation at an elevated temperature, but it appears less probable that such a change would occur in the biogenesis of the alkaloid. However this may be, we are unwilling to abandon the recognition of the significant degree of coincidence indicated above and, if II is valid, we suggest that the intramolecular change necessary has indeed occurred at some stage of the synthesis. The relation of *des*-base-D to dihydrostrychnidines-A and -D shows that the ring-system can be transformed under some circumstances. As illustrated above the dimethylhexane chain equates strychnine (II or III) with cinchonine and its use would imply a mere alteration in the order of coupling of the units from that contemplated in 1917.

Constitution of the neo-*Bases*.—In order to provide a direct interpretation of the results of oxidation processes, Leuchs and Berger (*Ber.*, 1935, **68**, 290) suggested that the relation of double bond to N(b) in the *neo*-series is not that of an allylamine but of a vinylamine. In commenting on this Reynolds and Robinson (1935, *loc. cit.*) admitted the feasibility of the hypothesis but considered that the evidence was insufficient to justify a preference for one of the two possible views.

We have now found a diagnostic reaction which is decisive in favour of the vinylamine structure.

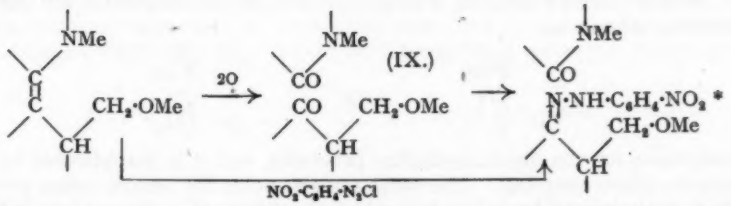
The *neo*-bases couple with diazonium salts in dilute aqueous acid solution and the precipitated yellow products are neutral and exhibit the properties of arylhydrazones. Evidently :N(b)· becomes :N(b)·CO· and the process, dependent on the reactivity of the hetero-enoid system, :N(b)·C=C·, is most simply represented as follows :

$$:N\cdot\dot{C}{=}\dot{C}\cdot \longrightarrow :N\cdot\dot{C}(OH)\cdot\dot{C}\cdot N_2\phi \longrightarrow :N{-}\dot{C}O\ \dot{C}\cdot N_2H\phi.$$

Whatever the mechanism of the reaction it must take a course analogous to that of the characteristic oxidation of the *neo*-bases which in several cases has been shown to result in the addition of two oxygen atoms, with the formation of keto-amides. Thus Briggs and Robinson (*loc. cit.*) oxidised methoxymethyldihydro*neo*strychnine (VIII) to the neutral ketone methoxymethyl*chano*dihydrostrychnone (IX) in almost quantitative yield by means of perbenzoic acid.

The *p*-nitrophenylhydrazone of IX is identical with the product obtained by coupling VIII with *p*-nitrobenzenediazonium chloride.

(VIII.)



(IX.)

The methyl-ψ-strychnidine of Clemo, Perkin, and Robinson (*loc. cit.*) was later shown to be *neo*strychnidine (Achmatowicz, Perkin, and Robinson, *J.*, 1932, 486); its oxidation by permanganate to strychnidone is doubtless fully analogous and the same applies to brucidone (Gulland, Perkin, and Robinson, *loc. cit.*). The substance termed diketo*neo*strychnine (Kotake and Yokoyama, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 321) obtained by oxidation of *neo*strychnine with permanganate represents another example It is better termed

* These formulæ are based on interpretations already advanced and have no significance beyond illustration of the text.

strychnone * (it is not derived by the conversion $2CH_2 \longrightarrow 2CO$, but by addition of 2O). We find that its *p*-nitrophenylhydrazone may also be obtained by the action of *p*-nitrobenzenediazonium chloride on *neo*strychnine. It may be noted that the *neo*-bases have also been oxidised so as to add two hydroxyl groups or one oxygen atom to the molecule; the constitution of these products is under investigation. We have described the above scheme as the simplest available and it is directly applicable to the appropriate derivatives of II, but not to those of III. Nevertheless it is clearly necessary to consider less obvious alternatives before we can reject III on these grounds, in view of its advantages in the other directions already indicated. A vinylamine group including N(b) in III could have three positions; the double bond moving to C_1C_2, C_3C_4, or C_5C_6.

(III.)

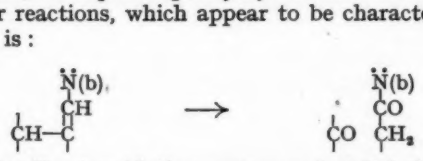
The positions C_1C_2 and C_5C_6 require that the oxidation products of the *neo*-bases should be aldehydes.

Although these substances are obtained by permanganate oxidations and have never been oxidised to acids by addition of an oxygen atom, it is just possible that the aldehyde group is sterically protected to a sufficient extent. Reynolds and Robinson (*loc. cit.*) considered the possibility that methoxymethyl*chano*dihydrostrychnone is an aldehyde because of the reactivity of the substance, its power of reducing ammoniacal silver solution, and the fact that the corresponding strychnane (but not the strychnone) affords a molecule of acetic acid in the Kuhn–Roth process. They decided against the aldehyde hypothesis because the strychnone was found to be stable to mercuric oxide in a boiling alcoholic suspension. Perhaps this experiment was inconclusive and the matter is at present being further studied.

The oxidation of a group $:N(b)\cdot CH{=}\dot{C}\cdot$ at C_3C_4 and C_5C_6 could give $:N(b)\cdot CHO\ CO:$; the question therefore arises as to whether it is conceivable that the oxidation products are substituted formamides. The answer is that the *N*-formyl group has not yet been detected. In submitting methoxymethyl*chano*dihydrostrychnone to the Clemmensen reaction, whereby the corresponding strychnane was formed, Reynolds and Robinson (*loc. cit.*) heated the substance with a large excess of concentrated hydrochloric acid for 29 hours. Again, an *N*(b)-formyl derivative is known in formylmethoxytetrahydrostrychnidine-B (Perkin and Robinson, *J.*, 1929, 992) and this is hydrolysed to a secondary amine by boiling sulphuric acid (10% by vol.) in 1 hour although it was found to be unchanged after attempted fission by alcoholic sodium ethoxide at 100°. This substance evolves carbon monoxide on heating but none could be obtained in this way, or on heating with concentrated sulphuric acid, from methoxymethyl*chano*dihydrostrychnone. When this substance is treated with phenylmagnesium bromide and the product decomposed, there is no evidence of the formation of benzaldehyde. If a formamide grouping is present, it must be endowed with quite remarkable stability.

The only other loophole that we can devise is illustrated in the scheme:

The inherent probability of such a transformation is not great, but it must be taken into consideration. Such an α-keto-amide group is contained in diketonucidine, dihydrostrychninone, strychninonic acid, and brucinonic acid. In all these cases the action of barium peroxide in the presence of barium hydroxide effects facile decomposition and barium carbonate is precipitated. That does not occur in a similar fashion with strychnone or methoxymethyl*chano*dihydrostrychnone. Moreover the *p*-nitrophenylhydrazones of these substances exhibit colour reactions which are almost exactly the same as those of the corresponding derivatives of simple ketones. Under the same conditions the *p*-nitrophenylhydrazones of the undoubted α-keto-amides listed show quite different intense colour reactions, which appear to be characteristic for this class of compounds. An apparently alternative scheme is:



This might be acceptable for the direct oxidation processes, but it is inapplicable to the formation of the nitrophenylhydrazones by diazo-coupling. The same remark holds for certain other possibilities and it must be recognised that the ketonic (or aldehydic) carbonyl is derived from the carbon atom in the β-position to N(b).

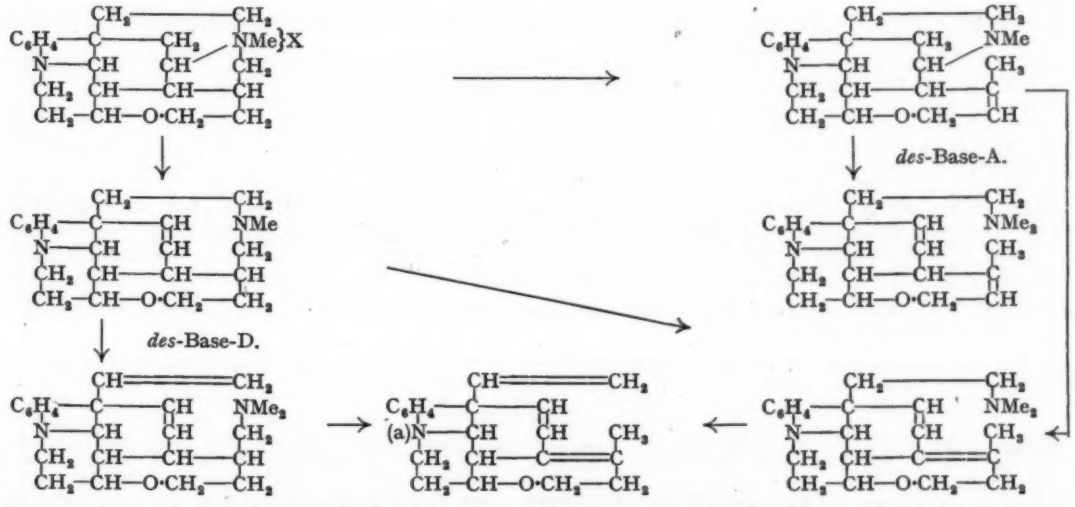
Reviewing these alternatives we do not favour the indirect mechanisms for the oxidations and it seems that the strychnones are unlikely to prove to be formamides. Hence the double bond in the *neo*-series is not thought to be in positions C_3C_4 and C_5C_6 of III. The acceptance of III with the *neo*-unsaturation at C_1C_2 is therefore dependent on the eventual recognition of the strychnones as aldehydes.†

* Our use of the term "strychnone" dates from 1937 (strychnidone still earlier) and we deprecate its employment in a different connexion (Leuchs and Räck, *Ber.*, 1940, **73**, 731), especially for the substance $C_{21}H_{20}O_3N_2$ which is not a ketone.

† The C_1C_2 position is, however, highly improbable for stereochemical reasons.

The vinylamine character of the *neo*-bases has certain other consequences. The allyloid hypothesis, formerly invoked in explanation of the ready reconstitution of quaternary salts from methoxymethyldihydro-*neo*strychnidine by the action of acids ($:NMe(b)\,CH_2(OMe)\cdot \longrightarrow :\overset{+}{N}Me\cdot CH_2\cdot$) and the contrast with the difficulty experienced in effecting the same change with the dihydro-derivative, must now be abandoned. In its place we may postulate: (*a*) the presence of free base in the acid solutions of the *neo*-derivative, or (*b*) the formation of a butadienoid intermediate and subsequent ring-closure [$:N(b)\cdot\dot{C}:\dot{C}—\dot{C}H—CH_2\cdot OMe \longrightarrow :N(b)\cdot\dot{C}:\dot{C}\cdot\dot{C}:CH_2 \longrightarrow :\overset{+}{N}(b)\cdot\dot{C}H\cdot\dot{C}:\dot{C}—CH_2$]. In connexion with (*a*) it has been frequently observed that *neo*strychnine is a much weaker base than strychnine. This is in accord with anticipation unless the hetero-enoid system functions so as to develop a quaternary salt ($:N\cdot\dot{C}=\dot{C}\cdot \longrightarrow :\overset{+}{N}=\dot{C}—\dot{C}H\cdot$), an unlikely event in view of the bridgehead double bond that would be formed. No alteration of the current view of the position of methoxylating fission is desirable and the only observation inconsistent with the *neo*-bases theory outlined above is that methyl*neo*strychnidinium chloride affords methyl*chano*dihydro*neo*strychnidine (*des*-base-A) on reduction with sodium amalgam (Perkin, Robinson, and Smith, *J.*, 1932, 1239). The specimen used was available and found to be wrongly labelled; the *neo* having been added to the name. The authentic material yields no *des*-base-A on reduction, but is converted into methyldihydrostrychnidinium-A chloride. It is therefore probable that *des*-base-A is methyl-*chano*dihydrostrychnidine. The reduction of *neo*strychnine to dihydrostrychnine already afforded a proof that the skeleton is unaltered in the passage to the *neo*-series. The present observation is confirmatory. Naturally the allylamine hypothesis still applies to the reductive fission.

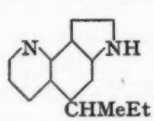
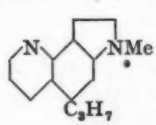
The course of the Hofmann process is best represented as shown below and it will be seen that III for strychnine could have been used and would give the same products at the first stage in the D-series and at the second stage in the A-series.



The two lower double bonds in the last formula, which represents one possibility for *des-aza*strychnidine-a or -b, can move into two positions nearer to N(a). Admittedly the *des*-base-A series could be formulated in a different way at the second stage but the representation given is the simplest and is in good agreement with the facts.

Changes in the nomenclature of the two second stage *des*-bases from *des*-base-A may well await confirmation of the structure proposed for *des*-base-A, experiments in relation to which are in progress.

It may be added that the constitutions of vomipyrine indicated by III for strychnine are X and XI (cf. Wieland and Horner, *Annalen*, 1937, **528**, 73). In XI both propyl and *iso*propyl groups are possible.

(X.)  (XI.) 

Our view of the present status of the structure III has been fully explained. A formula for vomicine on this basis cannot be excluded, and since a part of the skeleton II is transformed to that of III in the degradation of strychnine to β-collidine a similar change of the ring system is conceivable during the formation of vomipyrine (vomicine based on II).

In order to avoid misunderstanding we add the following summary of conclusions.

(1) The *neo*-bases are vinylamine derivatives.

(2) The structure III exhibits a more direct relation with cinchonine than II, and a more direct explanation of the formation of β-collidine on degradation.

(3) The available evidence bearing on the problem is insufficient and a decision cannot yet be made with confidence.*

Experimental.

p-*Nitrophenylhydrazone of Strychnone.*—*neo*Strychnine (2·0 g.) was dissolved in hot N-hydrochloric acid (100 c.c.) and alcohol added as the solution was cooled so as to prevent the crystallisation of the hydrochloride. Crushed ice and a solution of diazotised *p*-nitroaniline (2 g.) were added with mechanical stirring. A yellow precipitate separated and after an hour this was collected, washed, and dried in a vacuum over sulphuric acid (2·6 g.). The product was not easily crystallised and behaved like a mixture of stereoisomerides. In preliminary trials some crystals were obtained and these were used to seed a concentrated solution in acetone which was allowed to evaporate slowly in the refrigerator. A crust of yellow prisms separated and the substance was recrystallized in a similar manner, m. p. 269—271° (decomp.) (Found : C, 64·6; H, 5·6; N, 14·1. Calc. for $C_{27}H_{27}O_5N_5$: C, 64·7; H, 5·4; N, 14·0%). A specimen prepared from strychnone (Kotake *et al.*, *loc. cit.*) had the same properties, m. p., and mixed m. p. The addition of potassium hydroxide to a dilute alcoholic solution produces a bright cherry-red coloration with bluish nuance in thin layers; the coloration in acetone is very slightly bluer. The same coloration was noted in the case of the *p*-nitrophenylhydrazone of 4-methoxy-*cyclo*hexanone but the *p*-nitrophenylhydrazones of diketonucidine, strychninonic acid, and dihydrostrychninone gave quite distinct results. In all these cases the colour was purplish-violet.

p-*Nitrophenylhydrazone of Methoxymethyl*chano*dihydrostrychnone.*—(A) It suffices to triturate methoxymethyl*chano*-dihydrostrychnone (1·0 g.) and *p*-nitrophenylhydrazine (0·6 g.) in cold acetic acid (10 c.c.). After 24 hours, water (5 c.c.) was added and the solid collected. The product was twice crystallised from acetone as yellow prisms which shrank at 263° and decomposed at 266° to a red liquid (Found : C, 63·5; H, 6·0; N, 12·9. Calc. for $C_{28}H_{29}O_6N_5$: C, 63·6; H, 6·0; N, 12·8%). (B) *p*-Nitroaniline (7 g.) was dissolved by heating in concentrated hydrochloric acid (20 c.c.) and water (20 c.c.). Water (200 c.c.) and crushed ice were added and, with stirring, sodium nitrite (3·6 g.) in a little water. The diazo-solution measured 375 c.c. and 100 c.c. was added to a solution of methoxymethyldihydro*neo*strychnine (5 g.) in N-hydrochloric acid (50 c.c.). The yellow precipitate was very quickly formed and was collected after ten minutes, washed, and dried. It became crystalline on trituration with a little cold acetic acid but a considerable amount (stereoisomeride ?) remained in the solution. The solid was crystallised twice from acetone and formed yellow, elongated prisms which showed the same behaviour on heating, alone or mixed, as the specimen made as described in (A) (Found : C, 63·4; H, 6·1%).

The coloration in alcohol and in acetone on the addition of potassium hydroxide was indistinguishable from that exhibited by the *p*-nitrophenylhydrazone of strychnone.

Reduction of neo*Strychnidine Methosulphate by Means of Sodium Amalgam.*—*neo*Strychnidine (5·0 g.) was dissolved in boiling benzene (100 c.c.) and distilled methyl sulphate (15 c.c.) added and the whole refluxed for 6 hours. The salt was dissolved in water (250 c.c.) and the aqueous solution separated and rendered slightly alkaline. It was filtered from a small amount of unchanged base, heated on the steam-bath, and treated with sodium amalgam (200 g. of 3%) with passage of a stream of carbon dioxide. After 8 hours the solution was diluted, filtered, and acidified to Congo-red with hydrochloric acid. It was then evaporated to dryness and the residue exhausted with boiling alcohol. The alcoholic solution was evaporated, the residual quaternary salt dissolved in water, and the iodide precipitated by addition of excess sodium iodide. This salt crystallised from water in arrow-shaped prisms, decomp. 340—350°, and was converted by means of silver chloride into dihydrostrychnidine-A methochloride which was identified by comparison with an authentic specimen and by conversion into methoxymethyltetrahydrostrychnidine; leaflets from xylene, m. p. 223°, alone or mixed with an authentic specimen (cf. Oxford, Perkin, and Robinson, *J.*, 1927, 2401).

One of us (H. T. O.) acknowledges gratefully the assistance of a Senior Demyship of Magdalen College, Oxford, and of a Senior Research award (D.S.I.R.).

Dyson Perrins Laboratory, Oxford University. [*Received, February 27th,* 1946.]

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199. *Strychnine and Brucine. Part XLIII. Cuninecarboxylic Acid.*

By H. L. Holmes, H. T. Openshaw, and Sir Robert Robinson.

The oxidation of dihydrostrychninone (I) by means of barium peroxide affords cuninecarboxylic acid (II) which, on heating, gives a neutral *lactam*.

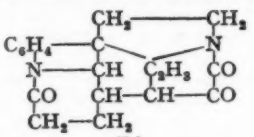
Publication of a paper by Prelog and Szpilfogel (*Helv. Chim. Acta*, 1946, **28**, 1669) prompts us to submit an account of experiments completed before the war and necessarily set aside during the past six years. The investigation has now been resumed with the object of effecting a meeting between degradation and synthesis on lines adumbrated in 1937 (Part XXXVI, *J.*, 941). The stage reached on the synthetical side is exposed in the following communications.

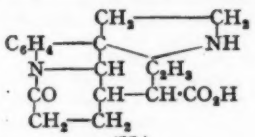
Dihydrostrychninolone-a (Leuchs, Diels, and Dornow, *Ber.*, 1935, **68**, 106) was oxidised to dihydrostrychninone (I) following Kotake and Mitsuwa (*Bull. Chem. Soc. Japan*, 1936, II, 238) and thence by means of barium hydroxide and hydrogen peroxide to *cuninecarboxylic acid* (II); the process is modelled on Leuchs's similar oxidation of strychninonic acid.

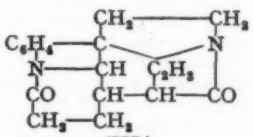
On heating at 210° and then at 260°, II loses water and yields the lactam (III) which is devoid of acidic and basic properties. Although cuninecarboxylic acid shows little tendency to lactamise under other conditions, and the temperature employed was high, this result favours the arrangement IV as against V in III. The possibility of a ring transformation is now being studied.

* (*Added, September 20th,* 1946).—An attempt made in the last few months to distinguish by a decisive experiment between II and III has given results, not yet free from all dubiety, but strongly supporting II. This statement applies only to the structural feature in regard to which II differs from III, and the full implications cannot be discussed until the work is completed.

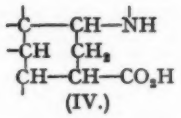
Prelog and Szpilfogel (*loc. cit.*) hydrolysed dihydrostrychninone to a hydrated keto-acid which lost carbon dioxide and water on heating with pyridine. The resulting aldehyde formed semi-acetals [–CH(OR)–N:] with methanol and ethanol and therefore the ring containing N(b) is apparently at least six-membered. Here again, a ring transformation is not excluded, although it is less probable than in our case.

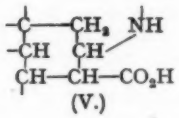

(I.)


(II.)


(III.)

Incidentally, if II had the constitution V we would anticipate scission of the β-amino-acid with formation of an αβ-unsaturated acid. There is no sign of such a process either on pyrolysis or, as has recently been observed by Mr. R. A. Hancock, on vigorous treatment with methyl sulphate and sodium hydroxide.


(IV.)


(V.)

Experimental.

Strychninonic Acid (cf. Leuchs and Schwaebel, *Ber.*, 1913, **46**, 3695).—Strychnine (7·5 g.) suspended in acetone (50 c.c.) and then finely powdered potassium permanganate (15 g.) were added to a vigorously stirred mixture of acetone (2500 c.c.) and chloroform (500 c.c.). At intervals of 30 minutes nine further similar additions of strychnine in acetone and permanganate were made and the mixture was finally stirred for an hour. The manganese precipitate was collected and washed with acetone (400 c.c.). It was then stirred with crushed ice (500 g.), saturated ammonium chloride solution (500 c.c.), and water (1200 c.c.) for 15 minutes and after filtration this extraction was twice repeated. Each extract was stirred with chloroform (200 c.c.) and acidified with hydrochloric acid, and the chloroform was separated and the solution extracted twice with fresh chloroform (300 c.c.). The whole chloroform solution (2700 c.c.) was concentrated to 300 c.c. and water (75 c.c.) added. The aqueous solution was then made alkaline by means of potassium hydrogen carbonate and stirred to ensure complete extraction. The aqueous layer was washed with chloroform (50 c.c.), just acidified with acetic acid, boiled to remove chloroform, and then made strongly acid with acetic acid. The product crystallised and was recrystallised from 160 parts of hot water as colourless plates (15·2 g.) (0·23 g. in 5·86 c.c. of N/10-NaOH made up to 25 c.c. with water; $[\alpha]_D^{20°}$ − 46·7°). Ten lbs. of strychnine were so worked up and the chloroformic solutions from which the strychninonic acid was extracted were combined and concentrated, when a white crystalline powder (55·0 g.) separated. This neutral *product* is sparingly soluble in alcohol and acetone, moderately readily soluble in acetic acid. It is soluble in 500 parts of hot water and crystallises on cooling in white, elongated prisms, m. p. 332° (vac.) (Found: C, 67·45, 67·40, 67·41; H, 5·28, 5·26, 5·35; N, 8·39, 8·26. $C_{19}H_{18}O_4N_2$ requires C, 67·41; H, 5·36; N, 8·28%) (0·10 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ − 14·2). Leuchs and Schwaebel (*loc. cit.*) describe the substance as browning at 290°, m. p. 320° (decomp.), and assign the composition $C_{19}H_{20}O_4N_2$ (C, 66·7, 66·8, 67·0; H, 5·7, 5·7, 5·5; N, 8·0, 8·3. Calc.: C, 67·1; H, 5·9; N, 8·2%). It is almost certain that the substances are identical. Our compound gives a typical Otto reaction and is soluble in concentrated hydrochloric acid. On addition of water a new substance separates, m. p. 350—354°, and this also gives an Otto reaction.

A crystallographic examination of strychninonic acid was kindly undertaken by Dr. D. P. Riley who reports as follows.

"The crystals consisted mainly of orthorhombic plates {010} elongated along [100]. *X*-Ray oscillation photographs were taken with the crystal set up about [100] firstly with the *X*-rays shining parallel to (010) and secondly parallel to (001). From these photographs the unit-cell dimensions were measured as approximately: *a*, 7·2 A.; *b*, 8·45 A.; *c*, 14·5 A.

"The density of the crystals as determined by flotation in a mixture of carbon tetrachloride and toluene was 1·462 ± 0·002 at 20° C. Hence if it is assumed that there are two molecules in the unit-cell, the molecular weight of the compound can be calculated to be 392 ± 5 ($C_{21}H_{20}O_4N_2$ requires *M*, 396)."

Methyl strychninonate, m. p. 247—249°, was obtained from the acid by Leuchs and Reich (*Ber.*, 1910, **43**, 2420) by short treatment with methanolic hydrogen chloride (2·5%).

We employed a 25% excess of diazomethane and an ethereal suspension of the acid. The product crystallised from methanol in slender needles, m. p. 246·4—246·7° (0·015 g. in 25 c.c. of methanol; $[\alpha]_D^{20°}$ − 166·6°).

Catalytic Reduction of the Neutral Product, $C_{19}H_{18}O_4N_2$.—The substance (0·75 g.) was reduced at 16°/760 mm. in acetic acid (100 c.c.) in the presence of platinum oxide (0·05 g.).

The theoretical volume of hydrogen (1 H_2) was absorbed in 45 minutes. The filtered solution was evaporated and the residue crystallised from water (0·70 g.). It was twice recrystallised from water (250 parts) and obtained as long, white needles, m. p. 244—245° (Found: C, 67·16, 67·01; H, 6·02, 5·90; N, 8·16. $C_{19}H_{20}O_4N_2$ requires C, 67·04; H, 5·92; N, 8·23%) (0·10 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ + 18·5°).

Catalytic Reduction of Strychninonic Acid.—The acid (1·66 g.) in acetic acid (120 c.c.) with platinum oxide (0·1 g.) absorbed the theoretical volume of hydrogen in 2¼ hours at 17°/740 mm. The product was crystallised from water and found to be pure dihydrostrychninonic acid (1·50 g.). The long glistening needles lost water of crystallisation at 100°/9 mm., m. p. 312° (decomp.) (0·30 g. in 7·6 c.c. N/10-NaOH made up to 25 c.c.; $[\alpha]_D^{20°}$ − 4·9°) (Found in anhydrous material: C, 63·2; H, 5·6; N, 7·2. Calc. for $C_{21}H_{22}O_6N_2$: C, 63·3; H, 5·6; N, 7·0%). Leuchs (*Ber.*, 1908, **41**, 1711) gives decomp. 315° and $[\alpha]_D^{20°}$ + 4·3° in 3·5% solution.

Dihydrostrychninone.—Strychninolic acid and strychninolone-a (Leuchs and Schneider, *Ber.*, 1909, **42**, 2495) were obtained by small modifications of the known methods in 82% and 93% yields respectively. The acid, long needles from water, lost solvent at 100°/9 mm. and had m. p. 238°; strychninolone-a formed elongated prisms from alcohol, m. p. 228° (0·59 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ − 115·3).

Dihydrostrychninolone-a (Leuchs, Diels, and Dornow *loc. cit.*), formed long needles, m. p. 271—272° (0·925 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 11·3°) (Found: C, 70·6, 70·5; H, 6·3, 6·2; N, 8·8, 8·7. Calc. for $C_{19}H_{20}O_3N_2$: C, 70·4; H, 6·2; N, 8·6%). On oxidation according to Kotake and Mitsuwa (*loc. cit.*) a 70% yield of a product crystallised from alcohol was obtained. This crystallised from alcohol in elongated prisms that consistently had m. p. 263—264° (Found: C, 70·6, 70·7; H, 5·8, 5·8; N, 8·7, 8·8. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%) (0·099 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 29·8°). The Japanese chemists gave m. p. 314° but it is not clear from the description that their starting point was pure strychninolone-a. However, the probability is that the lower-melting material was a labile stereoisomeride (dependent on :CH–CO—) because we, also, have recently observed the m. p. 314° and Prelog and Szpilfogel give the m. p. 318°, $[\alpha]_D^{20°}$ — 49° in chloroform.

Dihydrostrychninone, m. p. 263—264° (1·0 g.), in acetic acid (50 c.c.), along with platinic oxide (0·05 g.), was shaken with hydrogen at 17°/743 mm. The theoretical volume (95 c.c.) was absorbed in 24 minutes and absorption then ceased. The product crystallised from ethanol in long, colourless needles (0·95 g.), m. p. 271—272°, alone or mixed with dihydrostrychninolone-a (0·1 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 10·6°). This is a rather curious result in view of the reduction of strychninonic acid to dihydrostrychninonic acid (*v. supra*).

Cuninecarboxylic Acid (II).—Dihydrostrychninone (2·5 g.) was dissolved by gentle heating in aqueous barium hydroxide (60 c.c. of 5%); the cooled solution was treated with perhydrol (1·7 g.) in water (20 c.c.).

Barium carbonate was quickly precipitated and the reaction was completed by heating for 2 minutes on the steam bath. The mixture was made faintly acid with sulphuric acid, filtered, and extracted thrice with chloroform. The aqueous solution was then concentrated under reduced pressure to about 5 c.c. when 1·5 g. of a pale brown solid separated. The *substance* crystallised from water in dense, colourless prisms, that softened at 215°, hardened again, and then melted at 265—270° (Found: C, 69·2, 69·3; H, 6·6, 6·6; N, 8·9, 9·1. $C_{18}H_{20}O_3N_2$ requires C, 69·3; H, 6·5; N, 9·0%) (0·07 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 22°). The substance shows the characteristic behaviour of an amino-acid and exhibits a normal Otto reaction.

This acid (1·5 g.) was refluxed for 3 hours with methanol (30 c.c.) and sulphuric acid (0·5 c.c.). After addition of water and basifying, the *methyl* ester was isolated by extraction with chloroform. The derivative crystallised from methanol in prismatic needles, m. p. 167—168° (Found: C, 69·9; H, 6·7; N, 8·3. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·8; N, 8·6%) (0·07 g. in 25 c.c. of methanol; $[\alpha]_D^{20°}$ — 25°).

Cuninecarboxylic acid was heated under nitrogen at 210°, when it softened, and then at 260°. During 30 minutes the product sublimed, m. p. 290—291°. It crystallised from methanol in large plates, m. p. 296—297° (Found: C, 73·3, 73·4; H, 6·1, 6·1; N, 9·4. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1; N, 9·5%) (0·1 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 220°). This neutral *lactam* (III) exhibits the Otto reaction. An attempt to hydrogenate this lactam (0·4 g.) in the presence of platinic oxide (0·05 g.) was made but the hydrogen absorbed corresponded to the volume taken up by the catalyst. Consequently it does not appear to be unsaturated, but the experiment will be repeated.

Oxidation of Strychninolone-a by means of Chromic Acid.—Our results diverge from those of Kotake and Mitsuwa (*loc. cit.*).

A solution of chromic anhydride (1·0 g.) in water (4 c.c.) and acetic acid (100 c.c.) was slowly added to one of strychninolone-a (5·0 g.) in acetic acid (60 c.c.) with vigorous stirring. Half an hour after the last addition the solution was poured into water (2000 c.c.) and extracted with chloroform (3 × 150 c.c.), and the extract washed with water and aqueous sodium bicarbonate. The pale green solid residue, after removal of the solvent, was dissolved in alcohol (charcoal) and, on concentration of the solution, 4·3 g. of colourless crystals were obtained. After two recrystallisations the beautiful plates had m. p. 246—247° (corr.) (Found: C, 68·8, 68·7; H, 6·2, 6·1; N, 7·9, 7·6. $C_{21}H_{22}O_4N_2$ requires C, 68·8; H, 6·1; N, 7·7%) (1·0 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20°}$ — 127·3°).

The Otto reaction was characteristic and the *substance* is clearly $C_{19}H_{16}O_3N_2 + C_2H_6O$, containing the groups :NH(b) and ·CO·CO_2Et.

Kotake and Mitsuwa (*loc. cit.*) did not use alcohol but they manipulated the product with methanol and ethyl acetate and obtained strychninone, $C_{19}H_{16}O_3N_2$, m. p. 273°. Contamination with the methanol adduct is not indicated by the carbon content which was even 0·6% high.

On catalytic reduction under the conditions used in the case of dihydrostrychninone, the ring closed again, and, after absorption of a volume of hydrogen corresponding to $2H_2$, dihydrostrychninolone-a was obtained (m. p., mixed m. p., and rotation).

One of us (H. L. H.) is grateful for the award of a Parker Travelling Fellowship of Harvard University.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March 30th,* 1946.]

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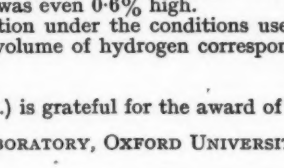
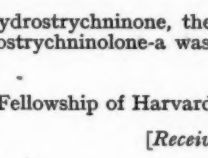
200. *Strychnine and Brucine. Part XLIV. Synthetical Experiments. Part II.*

By H. L. HOLMES, H. T. OPENSHAW, and SIR ROBERT ROBINSON.

Starting with the Leuchs degradation of strychnine (I) * further operations, possibly by way of cuninecarboxylic acid (cf. Part XLIII), might result in the production of the lactam (II). This substance has accordingly been synthesised by methods entirely analogous to those already developed for the preparation of a carboxy-derivative of II (Part XXXVI, Openshaw and Robinson, *J.*, 1937, 941).

(I.)



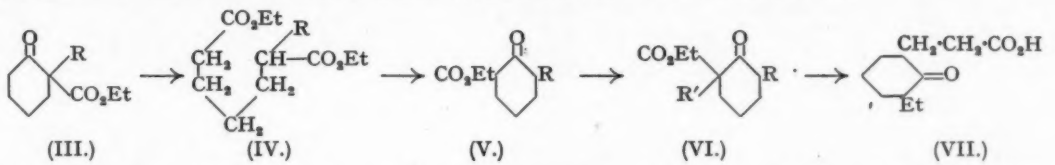


(II.)

The groups removed from I in the formation of cuninecarboxylic acid are indicated by the dotted lines in the formula.

* The older formula for strychnine is retained because it was the working hypothesis in this investigation.

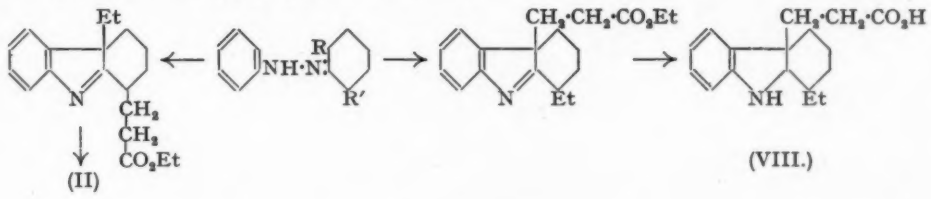
2-*Ethyl*cyclo*hexanone*-6-β-*propionic acid* (VII) has been obtained in accordance with the scheme below, in which R is Et and R′ is $CH_2{\cdot}CH_2{\cdot}CO_2Et$, or alternatively R is $CH_2{\cdot}CH_2{\cdot}CO_2Et$ and R′ is Et.



(III.) (IV.) (V.) (VI.) (VII.)

The transformation of III to V was in part direct under the influence of alcoholic sodium ethoxide (cf. Part XXXVI, *loc. cit.*); the intermediate product (IV) was, however, also isolated, and converted into V by means of sodium.

The *ethyl* ester of VII was condensed with phenylhydrazine and then changed by the action of alcoholic hydrogen chloride into a mixture of indolenines, which were not separated and purified but catalytically hydrogenated. It was then possible to isolate the *lactam* of 11-*ethylhexahydrocarbazole*-1-β-*propionic acid* (II) and 1-*ethylhexahydrocarbazole*-11-β-*propionic acid* (VIII).



(II) (VIII.)

Experimental.

Ethyl 6-*Ethyl*cyclo*hexanone*-2-*carboxylate*.—A mixture of ethyl 2-ethyl*cyclo*hexanone-2-carboxylate (98 g.; cf. F. E. King, Barltrop, and Walley, *J.*, 1945, 279) and alcoholic sodium ethoxide (11·5 g. of sodium in 140 c.c.) was refluxed for 8 hours. After cooling, dilution with water, and acidification, the oil was collected by means of ether. Distillation afforded (1), 40 g., b. p. 122—125°/9 mm., and (2) 60·6 g., b. p. 135—141°/9 mm. On redistillation (1) had b. p. 122—123°/9 mm. and gave an intense violet coloration with ferric chloride in alcoholic solution; (2) had b. p. 137—138°/9 mm. ($n_D^{20°}$ 1·4682) (Found: C, 64·2; H, 9·7. $C_{13}H_{24}O_4$ requires C, 63·9; H, 9·8%).

This *ethyl* α-*ethylpimelate* (20 g.) in benzene (300 c.c.) was refluxed with granulated sodium (3 g.) for 6 hours. The isolated product had b. p. 122—123°/9 mm. ($n_D^{20°}$ 1·4690) and gave an intense ferric reaction (Found: C, 66·3; H, 9·2. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%). In addition to 16·0 g. of this *ethyl ethyl*cyclo*hexanonecarboxylate*, identical with the product obtained directly, there were isolated 4·0 g. of unchanged ester, b. p. 137—138°/9 mm.

Hydrolysis of ethyl α-ethylpimelate by means of aqueous alcoholic potassium hydroxide and acidification furnished α-ethylpimelic acid which crystallised from benzene–light petroleum (b. p. 40—60°) in prisms, m. p. 41—43°.

Ethyl 6-*Carbethoxy*-2-*ethyl*cyclo*hexanone*-6-β-*propionate*.—Ethyl 6-ethyl*cyclo*hexanone-2-carboxylate (12·0 g.) was converted into a gelatinous sodio-derivative by means of granulated sodium (1·4 g.) in boiling benzene (60 c.c.) during 2 hours. Ethyl β-chloropropionate (9·0 g.) was added to the cooled mixture which was then refluxed for 5 hours. The isolated product gave (1) b. p. 175°/10 mm., 1·8 g., (2) b. p. 183—188°/10 mm., 12·1 g., and a small amount of oil of higher b. p. The main fraction, on redistillation, had b. p. 184—185°/10 mm.; $n_D^{20°}$ 1·4582 (Found: C, 64·7; H, 8·6. $C_{16}H_{28}O_5$ requires C, 64·4; H, 8·7%).

The ethyl α-ethylpimelate, obtained as already described, may conveniently be employed. A solution of the ester (64·0 g.) in benzene (300 c.c.) was refluxed with granulated sodium (6·1 g.) until the metal disappeared. Ethyl β-chloropropionate (40·0 g.) was introduced and refluxing continued for 6 hours. The yield was 60·2 g., b. p. 182—184°/9 mm., and a few g. of unchanged ester were recovered.

Ethyl 6-*Carbethoxy*-6-*ethyl*cyclo*hexanone*-2-β-*propionate*.—Ethyl 6-carbethoxy*cyclo*hexanone-2-β-propionate (13·5 g.) (Openshaw and Robinson *loc. cit.*) was refluxed with benzene (40 c.c.) and granulated sodium (1·15 g.) until the metal disappeared. Ethyl iodide (6·0 g.) was added and refluxing continued for 3 hours. The product (14·9 g.), isolated in the customary manner, had b. p. 185—187°/10—11 mm. ($n_D^{20°}$ 1·4662) (Found: C, 64·2; H, 8·2. $C_{16}H_{28}O_5$ requires C, 64·4; H, 8·1%). On hydrolysis with boiling concentrated hydrochloric acid for 20 hours, 8·0 g. of this *ester* afforded 4·1 g. of ethyl*cyclo*hexanonepropionic acid. This crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 80—80·4°, alone or mixed with the acid obtained as described below. The ethyl ester had b. p. 149—150°/10 mm.; $n_D^{20°}$ 1·4599.

2-*Ethyl*cyclo*hexanone*-6-β-*propionic Acid* (VII).—Ethyl 6-carbethoxy-2-ethyl*cyclo*hexanone-6-β-propionate (100 g.) was refluxed for 24 hours with hydrochloric acid (760 c.c.; *d* 1·17), allowing alcohol to escape at 3-hourly intervals. On cooling, the acid separated in white, glistening plates and a little more was obtained by concentration of the solution (yield, 55 g., m. p. 74—78°). The *acid* crystallised from light petroleum (b. p. 60—80°) in glistening plates, m. p. 80—80·4° (Found: C, 66·7, 66·6; H, 9·3, 9·2. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·2%) (Equiv., N/100-NaOH, 194·5. Theory, 198). The sodium salt is rather sparingly soluble and crystallises from water.

The *ethyl* ester was prepared by slow distillation of a mixture of the acid (18·5 g.) with ethanol (11 c.c.), carbon tetrachloride (35 c.c.), and 8 drops of sulphuric acid. The isolated product (14·0 g.) had b. p. 157°/15 mm., 149—150°/9—10 mm.; $n_D^{20°}$ 1·4600 (Found: C, 69·3; H, 9·7. $C_{13}H_{22}O_3$ requires C, 69·1; H, 9·8%).

Lactam of 11-*Ethylhexahydrocarbazole*-1-β-*propionic Acid* (II).—A mixture of ethyl 2-ethyl*cyclo*hexanone-6-β-propionate (11·5 g.), phenylhydrazine (5·9 g.), and 4 drops of acetic acid was heated on the steam-bath for 2 hours. After addition of ether (200 c.c.), the solution was twice washed with water, dried (Na_2SO_4), and the solvent removed. The reddish coloured oily residue was taken up in alcohol (80 c.c.) and saturated with hydrogen chloride below 40°. Ammonium chloride soon separated and, when no more appeared to be formed, water was added and enough ammonia to give an alkaline reaction.

The oil was extracted with chloroform (3 × 150 c.c.), and the solution washed with water, shaken with norite, dried, filtered, and evaporated (residue, 14·0 g.).

This mixture of indolenines was dissolved in acetic acid (100 c.c.), platinic oxide (0·1 g.) added, and the solution shaken under hydrogen at 17°/753 mm.; 1060 c.c. were absorbed (theory, 1100 c.c.). The filtered solution was concentrated, added to water (1000 c.c.), and extracted with chloroform. The washed and dried extract was evaporated and the brown oily residue was refluxed for 3 hours with hydrochloric acid (30 c.c., *d* 1·17) and water (10 c.c.). The suspended oil was dissolved in chloroform (aqueous solution *A*, see below) and the solution was washed with water, dried, and distilled. After removal of the solvent, a viscous brown oil was obtained, b. p. 181—185°/0·32 mm. (4·9 g.). This set to a hard yellow resin but the *lactam* crystallised from methanol in feathery needles and then from ethyl acetate in elongated prisms, m. p. 106·8—107·5° (Found: C, 80·0, 80·0; H, 8·2, 8·2; N, 5·3, 5·4. $C_{17}H_{21}ON$ requires C, 80·0; H, 8·3; N, 5·5%). The Otto reaction was an intense purple coloration fading to brown.

1-*Ethylhexahydrocarbazole*-11-*β-propionic Acid* (VIII).—The aqueous acid solution (*A*, see above) was concentrated and cooled; dark brown crystals (1·82 g.) then separated. This material was recrystallised four times from dilute hydrochloric acid (charcoal) and obtained as colourless plates that softened at 265°, m. p. 271° (Found: C, 66·1; H, 7·9, N, 4·5, 4·4. $C_{17}H_{24}O_2NCl$ requires C, 65·9; H, 7·8; N, 4·5%). This *hydrochloride* exhibited no Otto reaction.

The free *amino-acid* was isolated by addition of ammonia to the aqueous suspension of the salt until solution occurred and then, on making just acid with acetic acid, the substance crystallised. It separated from aqueous alcohol as glistening plates, m. p. 156—157° (Found: C, 74·8; H, 8·4; N, 5·1. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·5; N, 5·1%).

11-*Ethyl*-1 : 9-*trimethylenehexahydrocarbazole*.—The above lactam (13·8 g.) in 60% sulphuric acid (200 c.c.) was reduced at a lead cathode in the usual apparatus (cf. *J.*, 1927, 1600). A current of 4·6 amps. (*ca.* 0·05 amp./cm.^{2}) was passed for 24 hours and the temperature was not allowed to rise above 20°.

The filtered solution was basified and the oily product collected by means of chloroform and distilled; b. p. 189°/16 mm. (9·1 g.). The base crystallised from methanol in glistening plates, m. p. 51·2° (Found: C, 84·3, 84·6, 84·6; H, 9·6; N, 5·8%). A weakly acid solution shows the strychnidine reaction, a red coloration on the addition of ferric chloride. With Ehrlich's reagent under the usual conditions it develops a blue coloration.

This is not, however, an indole reaction but is due to condensation in the *p*-position to nitrogen in the benzene nucleus. A similar reaction is exhibited by 1-alkyltetrahydroquinolines and by strychnidine.

A reagent was prepared by dissolving *p*-dimethylaminobenzaldehyde (1·2 g.) in alcohol (30 c.c.), hydrochloric acid (50 c.c., *d* 1·17), and water (50 c.c.). A mixture of the sample (8—10 mg.), alcohol (4 c.c.), and the reagent (1·5 c.c.) was heated on the steam-bath for 2 minutes.

No colour was developed with strychnine, dihydrostrychnine, methylstrychnine, ethoxymethyldihydro*neo*strychnine, dihydrostrychnidine-B, *iso*strychnine, dihydro*iso*strychnine, *iso*dihydrostrychnine, hexahydrostrychnine, methoxymethyltetrahydrostrychnidine, methoxymethyltetrahydrostrychnidine-B, brucine, dihydrobrucine, brucidine, β-colubridine, 9-methyltetrahydrocarbazole, and 9-methylhexahydrocarbazole.

A blue coloration developed with strychnidine, strychnidine methochloride, dihydro*iso*strychnidine, α-colubridine (intense greenish-blue), the base $C_{22}H_{30}N_2$ (Part XXV, p. 577), and the *des*-base-A from dihydrostrychnidine-A, m. p. 143°.

*neo*Strychnidine gave a pale greenish-blue, the base-*θ*, m. p. 192° (Part XXV, p. 579), gave a pale green, and methoxymethyldihydro*neo*strychnidine gave a pale blue coloration; tetrahydrostrychnine gave a bright greenish-yellow coloration. We are obliged to Professor Wilson Baker for making the above comparisons.

α-Colubridine gives an intense crimson coloration with ferric chloride (bluer than with strychnidine) whereas β-colubridine gives an orange-red, much weaker, coloration. Similarly strychnidine and α-colubridine develop orange-yellow to orange-red colorations when heated with various aldehydes (anisaldehyde, furfuraldehyde, veratraldehyde, vanillin) and hydrochloric acid, but β-colubridine does not exhibit these reactions.

After condensation with formaldehyde in acid solution the ferric reaction of α-colubridine is an intense bluish-violet coloration; that of β-colubridine remains unchanged by the preliminary treatment and hence the base does not condense with formaldehyde. The tests on the colubridines were carried out with solutions prepared by reducing the colubrines with amalgamated zinc and boiling concentrated hydrochloric acid. They are in harmony with the view that the reactions depend on condensations in the *p*-position to nitrogen in the benzene nucleus, and with the accepted constitutions of the colubrines.

The authors are grateful for the award of a Parker Travelling Fellowship to one of them (H. L. H.).

Dyson Perrins Laboratory, Oxford University. [*Received, April 6th,* 1946.]

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201. *Strychnine and Brucine. Part XLV. Synthetical Experiments. Part III.*

By H. T. Openshaw and Sir Robert Robinson.

The lactam of hexahydrocarbazole-1 : 11-ββ′-dipropionic acid (I) has now been obtained in stereoisomeric forms, one of which has been successfully submitted to the Schmidt reaction.

Attempts to resolve the resulting base (XVIII) have not yet been successful.

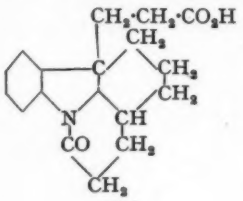
After trials in other directions 4-*carboxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionic acid* (III) has been synthesised from aliphatic intermediates and this has been transformed into a carboxy-derivative of I (II).

On bromination of the ester of III, followed by elimination of hydrogen bromide and hydrolysis, 6-*carboxy*-3 : 4-*dihydrocoumarin*-8-*β-propionic acid* (IV) was obtained. This acid had already been synthesised in the course of attempts to obtain III from aromatic imtermediates.

The work described in this communication and in Part XLIV was all carried out in 1937—1938 and necessarily set aside during the war; it has now been resumed.

In Part XXXVI (*J.*, 1937, 944) we described the synthesis of the lactam of hexahydrocarbazole-1 : 11-ββ′-dipropionic acid (I) and explained that we hoped to develop the synthesis of a 3-carboxy-derivative (II) of this substance. In order to apply the methods which we had developed for this purpose we required 4-carboxy-*cyclo*hexanone-2 : 6-ββ′-dipropionic acid (III) and the first route tried was by way of 6-*carboxy*-3 : 4-*dihydrocoumarin*-8-β-*propionic acid* (IV). It was hoped that the reduction of the benzene nucleus, hydrolysis, and oxidation would lead to the desired product, but the method failed because catalytic reduction of IV could not be effected.

The acid (IV) was synthesised as follows. *p*-Chlorophenol was condensed with formaldehyde in alkaline solution (G. P. 510,447; *Centr.*, 1931, I, 2115) and the chlorodi(hydroxymethyl)phenol thus obtained gave, on methylation, 4-*chloro*-2 : 6-*di*(*hydroxymethyl*)*anisole* which was oxidised to 4-*chloro*-2 : 6-*diformylanisole* (V) (cf. Ullmann and Brittner, *Ber.*, 1909, **42**, 2540, for the analogue from *p*-cresol). By condensation with malonic acid in pyridine solution, in the presence of piperidine, this was transformed into 4-*chloroanisole*-2 : 6-ββ′-*diacrylic acid* (VI), which on catalytic reduction yielded *anisole*-2 : 6-ββ′-*dipropionic acid* (VII). An attempt to introduce a carboxyl group into the 4-position of the *ethyl* ester of this compound by means of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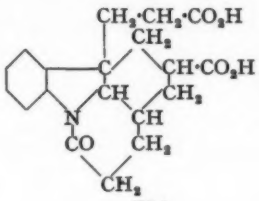
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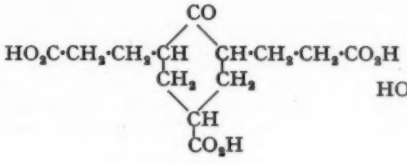
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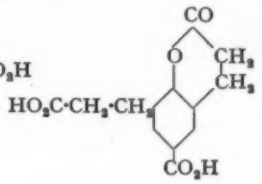
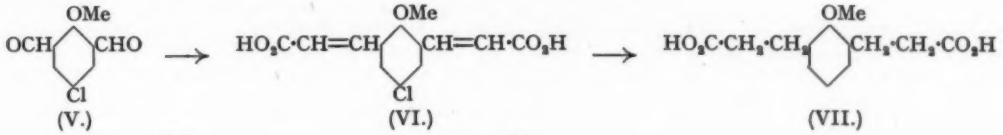
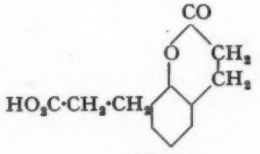

(IV.)

phenylethylcarbamyl chloride and aluminium chloride was unsuccessful. The Friedel–Crafts reaction with acetyl chloride gave a small yield of *ethyl* 4-*acetylanisole*-2 : 6-ββ′-*dipropionate*, characterised by its 2 : 7-*dinitrophenylhydrazone*, but, on account of the poor yield, the oxidation of this compound was not investigated.

On demethylation of the acid (VII) 3 : 4-*dihydrocoumarin*-8-β-*propionic acid* (VIII) was obtained. This substance could not be condensed with formaldehyde in alkaline solution; coupling with benzenediazonium chloride afforded benzeneazodihydrocoumarinpropionic acid, isolated as is *potassium* salt (IX). On reduction with sodium hydrosulphite an amine was obtained, which was converted into the corresponding nitrile by the Sandmeyer method, and thence into the desired acid (IV).

A more convenient method, however, involved the nitration of anisoledipropionic acid (VII); the resulting 4-*nitroanisole*-2 : 6-ββ′-*dipropionic acid* yielded 4-*aminoanisole*-2 : 6-ββ′-*dipropionic acid* on catalytic reduction, and this compound was diazotised and converted into the nitrile (X), which on treatment with hydrobromic acid afforded the acid (IV). The latter was converted into its *dimethyl* ester in the usual manner, but this substance was unaffected by shaking in acetic acid solution with hydrogen and platinic oxide, although ethyl *p*-acetoxybenzoate was readily reduced under the same conditions.


(V.) (VI.) (VII.)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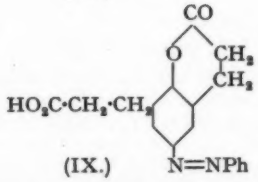
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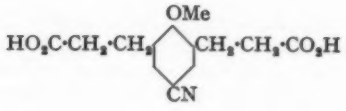
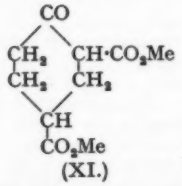

(X.)

A satisfactory synthesis of the keto-tricarboxylic acid (III) was devised on lines similar to those used for the synthesis of *cyclo*hexanonedipropionic acid (Part XXXVI, *loc. cit.*). The preparation of ethyl *cyclo*hexanone-2 : 4-dicarboxylate by the cyclisation of ethyl pentane-1 : 3 : 5-tricarboxylate has been described by Kay and Perkin (*J.*, 1906, **89**, 1647), but the method of preparation of the latter compound from ethyl 3-cyanopentane-1 : 3 : 5-tricarboxylate is inconvenient. In the present work pentane-1 : 3 : 5-tricarboxylic acid has been employed (Bottomley and Perkin, *J.*, 1900, **77**, 299).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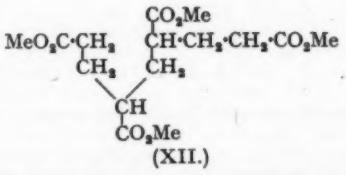
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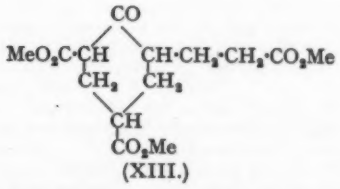
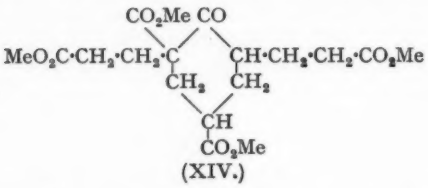

(XIII.)

The *methyl* ester of this acid, on treatment with sodium in benzene, afforded *methyl* cyclo*hexanone*-2 : 4 *dicarboxylate* (XI). When this ester was treated with methyl β-chloropropionate and sodium methoxide in methanolic solution, condensation and ring fission occurred, the product being *methyl heptane*-1 : 3 : 5 : 7-*tetracarboxylate* (XII). Treatment of the benzene solution of this ester with sodium methoxide brought about cyclisation to *methyl* 4 : 6-*dicarbomethoxy*cyclo*hexanone*-2-β-*propionate* (XIII) and the further action of methyl

β-chloropropionate on the sodium derivative of this compound produced *methyl* 4 : 6-*dicarbomethoxy*cyclo*hexanone*-2 : 6-ββ′-*dipropionate* (XIV). The methyl esters were employed on account of their lower boiling points.

When the ester (XIV) was hydrolysed, carbon dioxide was lost and the desired 4-*carboxy*cyclo*hexanone*-2 : 6-ββ′-*dipropionic acid* (III) was obtained.

The *ethyl* ester of III was converted into the methyl ester of the dihydrocoumarin derivative (IV) in the following manner. The substance readily reacted with two molecules of bromine in acetic acid solution, with evolution of hydrogen bromide. The resulting dibromo-ketone (XV) lost hydrogen bromide on heating and was converted into the corresponding phenolic compound (XVI), which was hydrolysed and converted into the methyl ester, identical with the methyl ester of IV.



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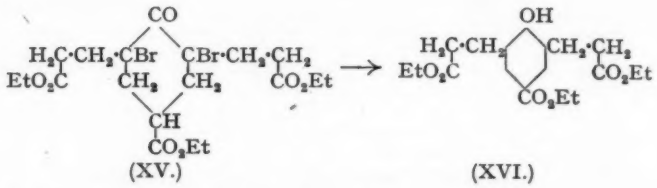
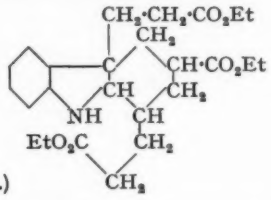


(XV.) (XVI.)

On treating the phenylhydrazone of the ethyl ester of III with alcoholic hydrogen chloride, reaction occurred with separation of ammonium chloride. The resulting tetrahydrocarbazolenine derivative was reduced by the addition of zinc dust, and a product was thus obtained which exhibited an Otto reaction. It could not be obtained in an analytically pure condition, however, and appeared to be a mixture of the desired ester of II possibly with the ester XVII. Hydrolysis of the ester afforded a small yield of the desired *acid* (II) in a crystalline condition, together with a considerable quantity of amorphous material, which was soluble in strong acid and was probably the acid corresponding to XVII. It underwent atmospheric oxidation in solution, with the production of a red coloration similar to that obtained by the oxidation of strychnidine derivatives.

A crystalline hydrazide could not be obtained by treatment of the ester with hydrazine hydrate. The application of the Schmidt reaction to the acid II has not yet been attempted.



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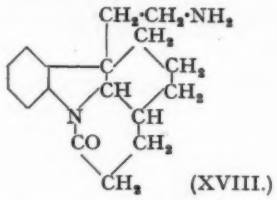
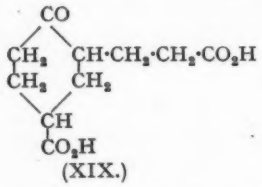


(XVIII.)

As a preliminary we have, however, applied this process to the acid I (Part XXXVI, *loc. cit.*) the method of preparation of which has been modified. In addition to the substance previously isolated (isomeride-A) we have obtained a new substance which is evidently a stereoisomeride (B). This is converted by hydrazoic acid and sulphuric acid into the *lactam-amine*-B (XVIII). The *hydrogen* d-*tartrate* crystallised without resolution.

The N-*dimethyl-base methiodide* was converted into the quaternary *d*-bromocamphorsulphonate, the examination of which will be continued. 4-*Carboxy*cyclo*hexanone*-2-β-*propionic acid* (XIX) has been prepared and converted by the Fischer reaction into the *lactam* of 3-*carboxytetrahydrocarbazole*-1-β-*propionic acid* (XX) and 3-*carboxytetrahydrocarbazolenine*-11-β-*propionic acid* (XXI).



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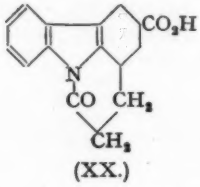

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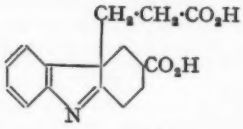

(XXI.)

The reduction of XXI gave a readily oxidisable oil which afforded a stable *acetyl* derivative.

Experimental.

4-*Chloro*-2 : 6-*di*(*hydroxymethyl*)*phenol*.—*p*-Chlorophenol (128 g.) was dissolved in aqueous sodium hydroxide (50 g. in 200 c.c.); formaldehyde (220 c.c. of 40%) was added, and the mixture kept at 30—40°. After 20 hours separation of a sodium salt commenced; after 48 hours it was collected, washed with a little water, and dried. The mother liquor, after being kept for 24 hours, yielded a further quantity of the sodium salt (total 180 g.). Acidification of the final mother liquor afforded some crude chlorodi(hydroxymethyl)phenol, which was purified by crystallisation from alcohol. A sample of sodium salt was dissolved in hot water and treated with dilute acetic acid, when the free chlorodi(hydroxy-

methyl)phenol was precipitated. After crystallisation it had the recorded m. p. 159—161° (*loc. cit.*) and gave an intense blue coloration with alcoholic ferric chloride.

4-Chloro-2 : 6-di(hydroxymethyl)anisole.—The crude sodium salt of chlorodi(hydroxymethyl)phenol (135 g.) was dissolved in boiling aqueous sodium hydroxide (12 g. in 500 c.c.), and methyl sulphate (70 c.c.) added at such a rate that the mixture, which was vigorously stirred, maintained itself at the boiling point. After the addition was completed, boiling was continued for 10 minutes, and the mixture was then allowed to cool, with stirring. The product was collected, washed with water, and dissolved in boiling water (1200 c.c.). The solution was decanted from a small amount of brown oil and boiled with norite. The oil was extracted with a further volume (500 c.c.) of boiling water, which was treated with the same norite. The combined filtered solutions, on cooling, deposited the product in long, colourless needles (56 g.), m. p. 127—128°. The *substance* was twice crystallised from water; m. p. 128° (Found: C, 53·2, H, 5·4. $C_9H_{11}O_3Cl$ requires C, 53·5; H, 5·4%).

4-Chloro-2 : 6-diformylanisole (V).—Recrystallised 4-chloro-2 : 6-di(hydroxymethyl)anisole (53 g.) was dissolved in boiling water (850 c.c.) containing sulphuric acid (40 c.c.), and a solution of potassium dichromate (50 g.) in water (130 c.c.) was gradually added with good shaking. The dialdehyde separated as an oil, which crystallised on cooling and was collected, washed with water, and dried. It retained chromic salts which gave it a green colour, but further purification was unnecessary for the next stage. The *substance* crystallised from acetic acid as colourless, long thin plates, m. p. 113—114°. Recrystallisation from light petroleum (b. p. 60—80°) raised the m. p. to 115—116° (Found: C, 54·1; H, 3·5. $C_9H_7O_3Cl$ requires C, 54·4; H, 3·5%).

4-Chloroanisole-2 : 6-ββ′-diacrylic Acid (VI).—A mixture of the crude dialdehyde (50 g.), malonic acid (57 g.), pyridine (120 c.c.), and piperidine (2 c.c.) was maintained at 70—90° for 24 hours. It was then heated until the separated solid had redissolved and poured into water (1000 c.c.) and concentrated hydrochloric acid (150 c.c.). The slimy, white precipitate was collected, washed, and dried (60 g.), and crystallised twice from acetic acid (or alcohol). The *acid* was obtained in colourless microscopic needles, m. p. 253—254° (Found: C, 55·7; H, 4·1. $C_{13}H_{11}O_5Cl$ requires C, 55·2; H, 3·9%).

Anisole-2 : 6-ββ′-dipropionic Acid (VII).—A solution of the pure diacrylic acid (29 g.) in aqueous potassium hydroxide (19 g. in 140 c.c.) was shaken with hydrogen and palladised strontium carbonate until the required volume of hydrogen (3 mols.) had been absorbed (4—12 hours). The filtered solution was acidified, when the *acid* (21 g.) was precipitated as a colourless oil which rapidly crystallised. It was recrystallised from water or ethyl acetate, forming colourless, flat prisms, m. p. 121—122° (Found: C, 62·1; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%).

Ethyl Anisole-2 : 6-ββ′-dipropionate.—The above acid (24·5 g.) was dissolved in a mixture of carbon tetrachloride (100 c.c.), alcohol (20 c.c.), and concentrated sulphuric acid (1 c.c.), and the solution was boiled under the automatic separator (*Org. Synth.*, Coll. Vol. I, 256) until water ceased to separate. The *ester* was isolated in the usual manner, b. p. 175—176°/0·5 mm. (22 g.) (Found: C, 66·0; H, 7·8. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·8%).

Ethyl 4-Acetylanisole-2 : 6-ββ′-dipropionate.—A mixture of the above ester (6 g.), acetyl chloride (3 g.), and carbon disulphide (50 c.c.) was treated with aluminium chloride (6 g.) in portions, with cooling in a freezing mixture. After standing at room temperature for 2 hours the mixture was refluxed for 18 hours; hydrogen chloride was slowly evolved. After the product had been decomposed with ice and hydrochloric acid, the resulting oil was isolated by means of ether and distilled. The greater part had b. p. 171—180°/0·3 mm., but a small fraction (0·5 g.) was collected at 220°/0·3 mm.; and on standing this partially solidified. It yielded a 2 : 4-*dinitrophenylhydrazone*, which crystallised from alcohol as orange leaflets, m. p. 128—129° (Found: C, 56·5; H, 5·6. $C_{25}H_{30}O_9N_4$ requires C, 56·6; H, 5·7%).

3 : 4-Dihydrocoumarin-8-β-propionic Acid (VIII).—Anisoledipropionic acid (5 g.) was heated with hydrobromic acid (25 c.c., *d* 1·5) at 140—150° under reflux for 6 hours. On cooling, the clear yellow solution deposited orange crystals (4 g.), and after recrystallising from ethyl acetate, the *acid* was obtained as salmon-pink plates, m. p. 142—143° (Found: C, 65·2; H, 5·2. $C_{13}H_{12}O_4$ requires C, 65·4; H, 5·4%).

Potassium 6-Benzeneazo-3 : 4-dihydrocoumarin-8-β-propionate (IX).—The above acid (1·5 g.) was dissolved in aqueous potassium hydroxide (2·3 g. in 12 c.c.) and heated on the steam-bath for a short time to ensure complete hydrolysis of the lactone grouping. The solution was then cooled in a freezing mixture and treated with a diazotised solution of aniline (0·63 g.). On neutralisation of the resulting deep orange solution, an orange crystalline solid separated. After crystallisation from water it had m. p. 187° (Found: C, 52·9; H, 4·8. $C_{18}H_{17}O_5N_2K,H_2O$ requires C, 52·8; H, 4·8%). On acidification of the solution of this *salt*, benzeneazodihydrocoumarinpropionic acid is precipitated as a red gum.

6-Carboxy-3 : 4-dihydrocoumarin-8-β-propionic Acid (IV).—The potassium salt of the azo-compound (2·6 g.) was dissolved in hot water (10 c.c.), with the addition of sufficient potassium hydroxide to bring about solution, and was treated with sodium hydrosulphite in small portions until all the colour had disappeared and crystallisation commenced. The mixture was then cooled and the cream-coloured solid collected and dried (1·4 g.).

This substance was then heated with concentrated hydrochloric acid (2 c.c.) for ½ hour, diluted, and diazotised, and the diazo-solution was added to a solution of hydrated copper sulphate (1·5 g.) and potassium cyanide (1·5 g.) in water (10 c.c.). The mixture was kept at the boiling point until evolution of nitrogen had ceased, and was then cooled, filtered from cuprous salts, acidified with hydrochloric acid, and extracted several times with ether. On evaporation of the ether a brown oil remained, and on rubbing with water this crystallised. After recrystallisation from water it formed brown prisms, m. p. 152—154°, which contained nitrogen.

This substance was refluxed with concentrated hydrochloric acid for 6 hours. On cooling and diluting with water, a colourless crystalline solid separated which, after crystallisation from acetic acid, had m. p. 226—227°. It was identified with 6-carboxy-3 : 4-dihydrocoumarin-8-β-propionic acid obtained by the method described below.

4-Nitroanisole-2 : 6-ββ′-dipropionic Acid.—A mixture of anisoledipropionic acid (10 g.) and concentrated nitric acid (10 c.c., *d* 1·4) was gently warmed until a vigorous reaction ensued. The mixture was allowed to boil by the heat of the reaction for 5 minutes; the reaction then slackened, and water (20 c.c.) was added. On cooling, the *nitro*-derivative separated as an almost colourless crystalline solid; it crystallised from water (80 c.c.) in well-formed, very pale yellow needles (7·5 g.), m. p. 181—182° (Found: C, 52·4; H, 5·1. $C_{13}H_{15}O_7N$ requires C, 52·5; H, 5·0%).

4-Aminoanisole-2 : 6-ββ′-dipropionic Acid.—The nitro-acid (10 g.), dissolved in alcohol (80 c.c.), was shaken with hydrogen in the presence of platinic oxide until the calculated volume of hydrogen had been absorbed. After removal of the catalyst the solution was evaporated to dryness, when a light brown oil remained. This crystallised on scratching, and after recrystallisation from alcohol formed prisms, m. p. 143—145°, which turned brown on standing in air. The *amino-acid hydrochloride* crystallised in minute colourless prisms (7·7 g.), m. p. 250—251°, when a hot solution of the crude product in concentrated hydrochloric acid was allowed to cool; the salt is readily soluble in water (Found: C, 51·6; H, 5·9; N, 4·5. $C_{13}H_{17}O_5N,HCl$ requires C, 51·4; H, 5·9; N, 4·6%).

4-Cyanoanisole-2 : 6-ββ′-dipropionic Acid.—The foregoing amino-acid hydrochloride (4·6 g.) was dissolved in dilute hydrochloric acid (3 c.c. of concentrated acid and 20 c.c. of water), added to a warm solution of hydrated copper sulphate (4·5 g.) and potassium cyanide (6 g.) in water (30 c.c.), and then boiled gently for 15 minutes. The solution was acidified with hydrochloric acid and filtered hot. The red oil (3·7 g.), deposited on cooling, was isolated by means of ether; it

crystallised in contact with a little acetic acid. Recrystallisation from a small volume of acetic acid afforded colourless prisms of the *nitrile*, m. p. 120—121° (Found : C, 60·8; H, 5·5. $C_{14}H_{15}O_5N$ requires C, 60·7; H, 5·4%).

Methyl 6-*Carbomethoxy*-3 : 4-*dihydrocoumarin*-8-*β-propionate*.—The crude nitrile (3·7 g.) was refluxed for 6 hours with hydrobromic acid (15 c.c., *d* 1·5). On addition of water (10 c.c.) a reddish-brown solid separated (2·7 g.). This crystallised from acetic acid in microscopic leaflets, m. p. 224—226°. Two recrystallisations gave a colourless product, m. p. 228—229° (Found : C, 58·0; H, 5·1. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%). The acid was evidently still impure and was converted into its *methyl* ester. The crude acid (4·3 g.) was refluxed with methanolic hydrogen chloride (20 c.c.) for 6 hours and the product isolated, in the usual manner, as a colourless oil (2·4 g.), b. p. 210—211°/0·8 mm. It solidified on trituration with light petroleum (b. p. 60—80°), and crystallised from ethyl acetate as colourless prisms, m. p. 107° (Found : C, 61·6 ; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

Methyl Pentane-1 : 3 : 5-*tricarboxylate* (cf. Bottomley and Perkin, *loc. cit.*).—A mixture of ethyl malonate (414 g.), formalin (140 g. of 37%), and diethylamine (9 g.) was kept for 12 hours and then heated on the steam-bath for 7 hours. On seeding and keeping in the ice-chest, the oil largely crystallised. The solid (212 g.) was collected, washed with 50% alcohol (50 c.c.), thoroughly drained, and dried. A sample crystallised from 70% alcohol as silky needles of the recorded m. p. 53—55°.

The crude ethyl pentanehexacarboxylate (172 g.) was refluxed with concentrated hydrochloric acid (750 c.c.) with slow escape of alcohol. After 15 hours the clear solution was evaporated to dryness under reduced pressure and the residue was decarboxylated by heating at 200° for an hour. Pentanetricarboxylic acid (68 g. or 97%) crystallised on cooling and stirring; a sample was purified by boiling its aqueous solution with norite, filtering, and evaporating to dryness under reduced pressure. It then separated from acetone–chloroform as colourless crystals of the recorded m. p. 113—114°.

A mixture of the crude tricarboxylic acid (68 g.), methanol (70 c.c.), and sulphuric acid (10 c.c.) was heated in an oil-bath until the internal temperature was 100°. Methyl alcohol vapour was then passed through the mixture, the temperature being maintained at 100° (*Org. Synth.*, Vol. X, p. 48). The vapour was led away through a 25 cm. column, and the temperature at the top of this was observed. It rose at first to 75—80° owing to removal of water, and then slowly fell. When it had reached 65—66°, and about 500 c.c. of methanol had distilled, the process was stopped and the *ester* isolated in the usual manner, b. p. 162°/12 mm. (62·5 g., 75%) (Found : C, 53·6; H, 7·3. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%).

Methyl cyclo*Hexanone*-2 : 4-*dicarboxylate* (XI) (cf. Kay and Perkin, *loc. cit.*).—A mixture of methyl pentanetricarboxylate (62·5 g.), powdered sodium (5·9 g.), anhydrous benzene (300 c.c.), and a trace of methanol was refluxed on the steam-bath for 8 hours. It was then cooled and added to ice and dilute hydrochloric acid, the benzene layer was collected, and the aqueous layer was extracted twice with benzene. The combined benzene solutions were washed with dilute aqueous sodium bicarbonate and water, dried, and distilled. The colourless oil (48 g. or 88%), b. p. 145—147°/10 mm., slowly deposited large prisms and after trituration with a little light petroleum the solid had m. p. 40—44° (Found : C, 55·9; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The *ester* developed an intense violet coloration on treatment with alcoholic ferric chloride.

Methyl Heptane-1 : 3 : 5 : 7-*tetracarboxylate* (XII).—A solution of sodium (8·65 g.) in methanol (180 c.c.) was slowly added to a mixture of methyl *cyclo*hexanonedicarboxylate (80·5 g.), methyl β-chloropropionate (46 g.), methanol (60 c.c.), and sodium iodide (1 g.), with shaking and cooling in ice. The mixture was kept at room temperature for 48 hours, at the end of which time it was neutral to litmus. Most of the alcohol was then distilled, the residue added to ice-water (1000 c.c.), and the *product* isolated by means of ether and distilled. A colourless oil (100·4 g. or 80%) was collected at 168—175°/0·5 mm.; redistilled, b. p. 165°/0·3 mm.; ferric reaction negative (Found : C, 54·6; H, 7·2. $C_{15}H_{24}O_8$ requires C, 54·2; H, 7·2%).

Methyl 4 : 6-*Dicarbomethoxy*cyclo*hexanone*-2-*β-propionate* (XIII).—The foregoing ester (52 g.) was refluxed for 8 hours with a solution of sodium (4·4 g.) in methanol (60 c.c.). After being cooled, the resulting solution was poured into a mixture of ice-water (800 c.c.) and hydrochloric acid (20 c.c.) and the product isolated with ether. On distillation, 42 g. were collected at 173°/0·5 mm. as a colourless oil (Found : C, 55·6; H, 6·8. $C_{14}H_{20}O_7$ requires C, 56·0; H, 6·7%).

Methyl 4 : 6-*Dicarbomethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate* (XIV).—A mixture of powdered sodium (1·7 g.) benzene (20 c.c.), and methanol (3 c.c.) was heated until all the sodium had reacted. It was then cooled and the above keto-ester (22 g.) added. After being heated for 30 minutes, it was again cooled and methyl β-chloropropionate (9·2 g.) was added. After 12 hours the solution was refluxed for 30 minutes, cooled, and mixed with ice-water (50 c.c.). The benzene solution was distilled and 20·2 g. collected at 215—218°/0·5 mm.

It was found more convenient to combine the last two stages into a single process. Powdered sodium (6·95 g.) in benzene (200 c.c.) was treated with methanol (12 c.c.), and, when the reaction had slackened, methyl heptanetetracarboxylate (100·8 g.) was added, and the mixture refluxed for 6 hours. It was then cooled and methyl β-chloropropionate (37·5 g.), dissolved in benzene (50 c.c.), was added. After standing at room temperature overnight the mixture was refluxed for 3 hours, cooled, and the product isolated as before. The desired *ester* (91·4 g.) had b. p. 210—215°/0·35 mm. (Found : C, 55·9; H, 6·8. $C_{18}H_{26}O_9$ requires C, 56·0; H, 6·7%).

4-*Carboxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionic Acid* (III).—The foregoing ester (33·4 g.) was dissolved in concentrated hydrochloric acid (150 c.c.) and refluxed (air condenser) for 2 hours, the alcohol being allowed to escape. The solution was then evaporated to dryness under reduced pressure, when the *tricarboxylic acid* separated as colourless crystals (23·3 g.). A sample was recrystallised from ethyl acetate, when it formed colourless prisms, m. p. 167° (Found : C, 54·4; H, 6·3. $C_{13}H_{18}O_7$ requires C, 54·5; H, 6·3%).

In order to determine whether more than one isomer was present, a sample was fractionally crystallised from ethyl acetate, but all the crops had approximately the same m. p.; the last mother liquor deposited a small amount of amorphous material.

Ethyl 4-*Carbethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate*.—The crude acid obtained above (23 g.) was dissolved in a mixture of alcohol (24 c.c.), carbon tetrachloride (100 c.c.), and sulphuric acid (0·5 c.c.), and the solution was boiled in the usual apparatus until no further separation of water occurred. The isolated product gave 27 g. of the *ester*, b. p. 197—199°/0·3 mm. (Found : C, 61·6; H, 8·1. $C_{19}H_{30}O_7$ requires C, 61·6; H, 8·1%).

Oxidation of Ethyl 4-*Carbethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate*.—The ester (5 g.) was dissolved in acetic acid (15 c.c.), and a solution of bromine (4·4 g.) in acetic acid (22 c.c.) was slowly added, the mixture being kept at 40—50° and well shaken. Hydrogen bromide was evolved and the colour of the bromine was rapidly discharged. The resulting pale yellow liquid was poured into water (300 c.c.), and the precipitated oil was isolated by means of ether. When heated on the steam-bath the product readily lost hydrogen bromide; after 3 hours the decomposition was completed by heating for a short time at 210°/15 mm., and on distillation a viscous oil was collected at 205—214°/0·2 mm.; on redistillation a colourless oil, b. p. 205—209°/0·2 mm., was obtained which partially crystallised on standing to a low-melting solid.

This ester was hydrolysed by refluxing with concentrated hydrochloric acid (20 c.c.) for 4 hours; on cooling and diluting the resulting solution a gummy acid was precipitated, which crystallised on treatment with aqueous acetic acid. This compound (1 g.) was converted into the methyl ester by means of boiling methanolic hydrogen chloride, and the

ester, isolated in the usual manner, had b. p. 205°/0·3 mm. It solidified on cooling and after crystallisation from a little ethyl acetate had m. p. 107°, undepressed on admixture with an authentic specimen of methyl 6-carbomethoxy-3 : 4-dihydrocoumarin-8-β-propionate.

Lactam of 3-*Carboxyhexahydrocarbazole*-1 : 11-*ββ′-dipropionic Acid* (II).—A mixture of ethyl 4-carbethoxy*cyclo*hexanone-2 : 6-*ββ′*-dipropionate (10 g.), phenylhydrazine (2·9 g.), and acetic acid (0·1 c.c.) was heated on the steam-bath for 2 hours in a slow stream of nitrogen; reaction took place with separation of water. The product, an orange-coloured oil, was dissolved in chloroform, washed twice with water, and dried (Na_2SO_4). The chloroform was then removed and the residual oily phenylhydrazone was dissolved in alcohol (30 c.c.). Hydrogen chloride was passed into the solution, which was cooled at first, and then allowed to heat until reaction occurred with separation of ammonium chloride. Passage of hydrogen chloride was continued until the solution was nearly saturated. In order to reduce the tetrahydrocarbazolenine thus produced, zinc dust (10 g.) was added in small portions to the warm mixture, which was finally heated on the steam-bath under reflux for 3—4 hours; almost all of the zinc had then dissolved. After cooling, the resulting nearly colourless solution was poured into water (600 c.c.), and the precipitated oil was taken up in ether, washed twice with dilute hydrochloric acid and then with water, dried (Na_2SO_4), and the ether removed. The residual orange-coloured oil (8 g.) exhibited the Otto reaction; on treatment of a trace of the substance, dissolved in 80% sulphuric acid, with a drop of potassium dichromate solution, a violet coloration was produced, which faded to a rose-red. On distillation, the main fraction was collected at 230—250°/0·3 mm., and distilled again at 225—240°/0·3 mm. as a highly viscous pale yellow oil (Found : C, 68·4; H, 7·8. $C_{23}H_{29}O_5N$ requires C, 69·2; H, 7·3. $C_{25}H_{35}O_6N$ requires C, 67·4; H, 7·9%). (For another sample, b. p. 230°/0·3 mm. : Found : C, 69·75; H, 7·5%.) After distillation, the substance gives an extremely transient colour in the Otto reaction. When the distilled ester was hydrolysed by refluxing with concentrated hydrochloric acid, or with alcoholic potash, only dark-coloured amorphous products were obtained.

In a second experiment, the crude product was not distilled but hydrolysed by heating under reflux with hydrochloric acid (15 c.c.) and water (15 c.c.), until a clear solution was obtained. On cooling and standing for several days a pale brown solid separated from the red solution, and this was collected (1 g.) and washed with dilute hydrochloric acid and with water. After crystallisation from acetic acid it formed colourless microscopic prisms, m. p. 250—257°; a second crystallisation raised the m. p. to 257—258° (Found : C, 66·1; H, 6·6. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%). When the Otto reaction is applied to this *substance*, a deep blue-violet colour is first produced; this fades in a few seconds through a reddish-purple to a rose-red, which is stable for about a minute and then fades to a light brown. The colour changes are very similar to those given by strychnine, but take place more rapidly.

Lactam of Hexahydrocarbazole-1 : 11-*ββ′-dipropionic Acid. Modification of Method.*—Ethyl *cyclo*hexanonedipropionate (50 g.), phenylhydrazine (18·1 g.), and acetic acid (2 c.c.) were heated together on the steam-bath for 2 hours. The product was taken up in ether, washed several times with water, dried (Na_2SO_4), and the ether evaporated. The orange-coloured oily phenylhydrazone was dissolved in absolute alcohol (100 c.c.) and the solution saturated with hydrogen chloride. Separation of ammonium chloride commenced after a short time, the temperature being allowed to rise to about 60°. After the reaction was completed, the mixture was poured into a large excess of ice-cold aqueous ammonia, and the product isolated by means of ether. After removal of the ether, the oil was dissolved in acetic acid and reduced catalytically. The reduction is usually slow and it is often advantageous to add fresh catalyst (Adams's). Heating to about 30° was also resorted to in some cases.

After the theoretical volume of hydrogen had been taken up, the acetic acid was removed by evaporation under reduced pressure, and the residue boiled with concentrated hydrochloric acid for 1 hour. On adding an equal volume of water and boiling, the product crystallises (37 g. or 74%).

The crude product, a pink or light brown crystalline solid, was crystallised once from acetic acid containing about 20% of water (norite). It then had m. p. approx. 118° and was a mixture of stereoisomers. By continued fractional crystallisation from alcohol and acetic acid it was separated into two substances : A, m. p. 271°, undepressed on admixture with a specimen obtained by the original method (tin reduction), and B, m. p. 232° (Found : C, 72·2, 72·1, 71·8; H, 7·3, 7·0, 7·2; N, 4·7, 4·8. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7%). The new *isomer* B gives the Otto reaction.

Lactam of 11-β-*Aminoethylhexahydrocarbazole*-1-β-*propionic Acid B.* (XVIII).—The above acid (isomer B, 5 g.) was dissolved in concentrated sulphuric acid (10 c.c.), the solution warmed to 40°, and a chloroform solution of hydrazoic acid (1 equiv.) added slowly with mechanical stirring. Gas evolution ceased after about 2 hours, and the resulting mixture was poured on ice. The chloroform was separated and the solution filtered from a small quantity of unchanged material; on making alkaline with sodium hydroxide, an almost colourless oil (3·4 g.) separated, which was isolated by means of chloroform. A specimen distilled at approx. 220°/0·2 mm. as a very viscous, greenish oil which did not crystallise (Found : C, 75·2; H, 8·6; N, 10·1. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2; N, 10·4%).

The *hydrogen* d-*tartrate* was precipitated as a colourless, crystalline solid when the components were mixed in acetone solution. It was crystallised several times from water, when it was obtained in well-formed prisms, m. p. 201—203° with softening from 175° (Found, in material dried at 100°/15 mm. : C, 57·6; H, 6·8; N, 6·4; loss at 150°, 4·1. $C_{12}H_{28}O_7N_2,H_2O$ requires C, 57·5; H, 6·8; N, 6·4; H_2O, 4·1%). The base recovered from this salt showed no optical activity.

Lactam of 11-β-*Dimethylaminoethylhexahydrocarbazole*-1-β-*propionic Acid B Methiodide.*—The above base, purified through the tartrate, was heated under reflux on the steam-bath, with excess of methyl iodide and sufficient methanol to bring about solution, for 8 hours. The solution was then evaporated to dryness, and the residual gum on treatment with acetone crystallised. It was recrystallised from a small volume of water, when it was obtaind in colourless prisms (Found, in material dried at 100°/15 mm. : C, 52·2; H, 6·9; N, 6·2; I, 27·7; loss at 150°, 4·0. $C_{20}H_{29}ON_2I,H_2O$ requires C, 52·4; H, 6·8; N, 6·1; I, 27·7; H_2O, 3·9%). The quaternary *d*-bromocamphorsulphonate was prepared from the methiodide and silver *d*-bromocamphorsulphonate, which were mixed in equimolecular quantities in aqueous solution. After removal of the silver iodide, the solution was evaporated to dryness. The product crystallised on treatment with ethyl acetate, and was recrystallised from water, when it was obtained in small clusters of colourless prisms, m. p. 265°.

4-*Carboxy*cyclo*hexanone*-2-β-*propionic Acid* (XIX).—Ethyl 4 : 6-dicarbethoxy*cyclo*hexanone-2-β-propionate was hydrolysed by refluxing with concentrated hydrochloric acid for 3 hours; the resulting solution was evaporated to dryness under reduced pressure, when the residue crystallised. It was recrystallised from ethyl acetate; colourless prisms, m. p. 130° (Found : C, 56·4; H, 6·4. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The semicarbazone had m. p. 191° (decomp.).

Lactam of 3-*Carboxytetrahydrocarbazole*-1-β-*propionic Acid* (XX).—The above keto-acid (5 g.), phenylhydrazine (2·5 g.), and a little 50% acetic acid were heated together on the steam-bath for 1 hour. Dilute sulphuric acid (50 c.c. of 20%) was then added and the mixture heated to boiling. An almost colourless crystalline solid (0·7 g.) separated, and was collected, washed with dilute acid, and with water, and dried at 100°. It was crystallised from alcohol (25 c.c.) and then formed thin prisms with a greenish tinge, m. p. 257—262°; a second crystallisation raised the m. p. to 270—271° with slight previous sintering (Found : C, 71·6; H, 5·6. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

3-*Carboxytetrahydrocarbazolenine*-11-β-*propionic Acid* (XXI).—The acidic mother liquor from the above preparation was washed twice with ether, made alkaline with ammonia, washed again with ether, and neutralised with acetic acid. The resulting precipitate soon crystallised and was dried at 100° (4·3 g.). It was crystallised first from 50% acetic acid

and then from alcohol and formed almost colourless leaflets, m. p. 222° (decomp.) (Found: C, 66·8; H, 5·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9%).

On shaking with hydrogen and platinic oxide in acetic acid, reduction took place, but the oily product was unstable and rapidly darkened in air. On heating with acetic anhydride, and decomposing with water, a crystalline product was obtained, m. p. 209—210°. This *acetyl* derivative crystallised from ethyl acetate–light petroleum in prismatic needles, m. p. 214—215° (Found: C, 65·1; H, 6·6; N, 4·0. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·3; N, 4·2%). The substance is readily soluble in aqueous sodium carbonate and gives a rather fugitive Otto reaction, a bluish-violet coloration. In addition to this substance a small amount of a neutral product was obtained from the acetylation process. This was possibly a cyclic ketone but the amount obtained was insufficient for further study; it gave an Otto reaction.

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202. *The Kinetics of Absorption of Gases from an Air Stream by Granular Reagents.*

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A theoretical treatment is given of the kinetics of the removal of a gas from an air stream by passage through a column of granular solid with which it reacts or by which it is irreversibly adsorbed.

Various practically important relations are determined for typical systems and compared with those predicted theoretically. These relations include: (*a*) the escaping concentration as a function of time, column length, flow-rate and initial concentration, (*b*) the distribution of gas or reaction product in the column, and (*c*) the influence of granule size.

The independent parts played by capacity factors and rate factors are shown.

THE present paper is concerned with the uptake of a gas from a flowing air stream on passage through a bed of granular reagent or absorbent. Theoretical treatments of this problem have been made by several previous workers. Mecklenberg and Kubelka (*Z. Electrochem.*, 1925, **31**, 488) and Mecklenberg (*Kolloid-Z.*, 1930, **52**, 88) employed reasoning on somewhat similar lines to that of the present paper, but which applied only to the case of physical adsorption of the gas. Where comparison is possible the equations derived in the present work are generally similar in form to those of Mecklenberg and Kubelka, though the physical interpretation of the constants is different. Dubinin (*J. Russ. Phys. Chem. Soc.*, 1930, **62**, 683, 1947) introduced the properties of the adsorbent in a different way: his equations also have approximately the same form with respect to the thickness of the adsorbent layer and to the gas concentration.

Theoretical equations for the shape of the wave-front of unadsorbed gas in an adsorbent column were derived by Bohart and Adams (*J. Amer. Chem. Soc.*, 1920, **42**, 523). These workers, however, did not confirm their results quantitatively, or apply them to the treatment of the problem of "breakdown times." A rather different and more ambitious treatment, correlated with experimental data for the adsorption of carbon dioxide on charcoal, has been given more recently by Wicke (*Kolloid-Z.*, 1939, **86**, 167, 295) and by Weyde and Wicke (*ibid.*, 1940, **90**, 156).

The present paper seeks to obtain the relevant equations in the simplest possible form, and to relate them more directly than has hitherto been possible to experimental measurements. The inter-relation of the important variables has been studied in some detail for several different systems, so as to give a general understanding of the factors governing the behaviour of these systems.

In the theoretical treatment the uptake of the gas is assumed to be irreversible. This will be valid for a chemical reaction in which the gas is destroyed. It will also be a legitimate approximation for adsorption under those circumstances or in those parts of the system where the reverse reaction is negligible in comparison with the uptake.

Simple Approximate Treatment.

The following discussion is based upon assumptions which are not by any means exactly fulfilled in practice. It has the advantage, however, of introducing the important quantities and of yielding quickly and simply some of the most important relations between them.

Let a column of granular material of unit cross-section be traversed by a stream of air carrying gas which is to be removed by adsorption or by a chemical reaction.

Let c_0 be the concentration of this gas in the entering stream, l the distance from the point of entry to some given point in the column, c the concentration of the gas at the point l, and T the total time for which the column has been exposed to the stream. Initially, before any of the material has been used up, there will be a concentration gradient along the column, the concentration falling from c_0 at the point of entry at a rate depending on the speed at which the gas is removed. At a distance l along the column the gas will have been in contact for a time t, such that l/t is the linear rate of flow; t must be distinguished from T, the total time for which the stream has been passing. When a given element of the gas has been in contact for a time t, its concentration may be taken to have dropped to c, where

$$c = c_0 e^{-Kt} = c_0 e^{-Kl/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

L being the linear flow rate, and K a measure of the rate of adsorption or reaction. This assumes that the interaction follows the equation for a reaction of the first order. This supposition is likely to be rather closely

fulfilled, since the interaction rate will be governed either by diffusion, which will follow a first-order equation, or by the rate of a heterogeneous reaction, which will also do this, at least when the concentration of the reacting gas is small.

After time T, some of the material will have become saturated with adsorbed gas, or will have had some of its catalytic centres inactivated. The reaction time, t, will no longer be given by l/L, but by the time for which the element of gas reaching the point l has been in contact with *unexhausted* material. The exhaustion is gradual, and to obtain the complete relation between c, l, and T, the appropriate differential equation must be solved. Many of the essential results, however, may be obtained with the assumption that the region of saturation moves along the column with a constant speed.

With this simplification, the length of the unexhausted column up to the distance l is $l - bT$, where b is the rate of exhaustion.

Therefore $$t = (l - bT)/L$$

and $$c = c_0 e^{-K(l-bT)/L}$$

or $$c = c_0 e^{-Kl/L} \cdot e^{KbT/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

If λ is the total length of the column, then the concentration of the emerging gas is given by

$$c = c_0 e^{-K\lambda/L} \cdot e^{KbT/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

whence *log* c *increases in direct proportion to* T, the time of passage of the stream.

As will be shown, this relation is always roughly and sometimes rather closely fulfilled.

In practical applications it is customary to define a *service* or *breakdown time*, namely, the time from the beginning of flow at which a chosen concentration of gas (c') is reached in the effluent.

The breakdown time, τ, is then given by the equation

$$c'/c_0 = e^{-K\lambda/L} \cdot e^{Kb\tau/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and unless the column length is greater than a certain value, λ_c, given by

$$c'/c_0 = e^{-K\lambda_c/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

there would be an immediate " breakdown " (according to the arbitrary criterion).

Substitution of (5) in (4) gives

$$e^{Kb\tau/L} = e^{K(\lambda-\lambda_c)/L}$$

whence $$\tau = (\lambda - \lambda_c)/b.$$

Now b is the rate of exhaustion of the active centres. Whether this represents the saturation of adsorptive regions, consumption of chemically active centres or progressive poisoning of catalytic points, it will be proportional to the total amount of gas passing (*i.e.*, to c_0L), and inversely proportional to the number of active centres originally available. With appropriately chosen units therefore

$$b = c_0L/N_0$$

where N_0 is the initial number of active centres.

Therefore $$\tau = N_0(\lambda - \lambda_c)/c_0L \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The breakdown time should thus increase linearly with column length after a " critical length " has been passed. It should also be inversely proportional to the concentration of gas in the entering stream.

When the flow rate is varied, the column length being kept constant, a corresponding relation appears, there being a critical flow rate, L_c, for which breakdown is immediate. From (4) we have

$$\tau = \frac{\lambda}{b} + \frac{L}{Kb} \ln \frac{c'}{c_0}$$

$\tau = 0$ when $L = L_c$, whence

$$\frac{\lambda}{b} + \frac{L_c}{Kb} \ln \frac{c'}{c_0} = 0$$

Therefore $$L_c = -\frac{K\lambda}{\ln c'/c_0}$$

so that we may write $$\tau = \frac{\lambda}{b}[1 - L/L_c]$$

Since $b = c_0L/N_0$ we have

$$\tau = \frac{\lambda N_0}{c_0}\left[\frac{1}{L} - \frac{1}{L_c}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The critical length diminishes and the critical flow-rate increases as the value of K increases. In the limiting case of instantaneous reaction the breakdown time increases linearly with column length and is inversely

proportional to the flow rate. With slower chemical reactions the divergence from simple direct or inverse proportionality becomes greater.

More Detailed Theory.

We consider a zone of the column between two parallel cross-sections of the column dl apart and distance l from the boundary of the column by which the gas enters. The gas entering this zone will be at a certain concentration $c_{l,T}$, where T is the time for which the gas stream has been flowing. Some of this gas is taken up and partially saturates or inactivates a portion of the material; the gas leaves the section at a lower concentration $c_{l+dl,T}$. If the concentration gradient is $(\partial c/\partial l)_T$, then

$$c_{l+dl,T} = c_{l,T} + \left(\frac{\partial c}{\partial l}\right)_T . dl$$

Now the active centres are being used up continuously and, it being assumed that the rate of removal of the gas depends upon the number of active centres available, this rate decreases with time. Consequently, the magnitude of the concentration gradient also decreases with time. It also follows that the concentration of gas at any point in the column increases steadily with time up to c_0, when the column up to that point is completely broken down and removes none of the gas. The concentration of gas in the stream is thus a function both of the distance along the column and of the time for which the stream has been passing.

The total amount of gas entering the section in the time dT is

$$V . c_{l,T} . dT$$

where V is the volume of gas flow per unit time.

In the same time the amount of gas leaving the section is

$$V . c_{l+dl,T} . dT = V[c_{l,T} + \left(\frac{\partial c}{\partial l}\right)_T . dl]dT$$

The excess of the amount of gas entering over that leaving is then

$$-V\left(\frac{\partial c}{\partial l}\right)_T dl . dT$$

Part of this excess has reacted or been adsorbed, while the rest has gone to increase the amount of free gas in the section. Thus

$$-V\left(\frac{\partial c}{\partial l}\right)_T dl . dT = \text{amount adsorbed or destroyed} + \text{increase in amount of free gas.}$$

If x is the amount of gas dealt with per c.c. of material, then the amount dealt with in the time dT in the zone we are considering is

$$A . dl \left(\frac{\partial x}{\partial T}\right)_l dT$$

A being the cross-sectional area of the column. The increase in the total amount of free gas in the section in the same time interval is

$$A . dl \left(\frac{\partial c}{\partial T}\right)_l . dT$$

Hence we have

$$-V\left(\frac{\partial c}{\partial l}\right)_T dl . dT = A . dl \left(\frac{\partial x}{\partial T}\right)_l dT + A . dl \left(\frac{\partial c}{\partial T}\right)_l . dT$$

i.e.,

$$-V\left(\frac{\partial c}{\partial l}\right)_T = A\left[\left(\frac{\partial x}{\partial T}\right)_l + \left(\frac{\partial c}{\partial T}\right)_l\right]$$

Or if $V/A = L$, the linear velocity of the gas, we obtain

$$-\frac{\partial c}{\partial l} = \frac{1}{L}\left[\frac{\partial x}{\partial T} + \frac{\partial c}{\partial T}\right] \quad . . . . . (8)$$

This is the fundamental equation for the removal of gas in the column and is independent of any assumptions as to the particular mechanism by which the removal is brought about, or of the kinetics of the removal.

To proceed further we must introduce an expression for the rate of removal of gas from the stream, and to obtain a reasonably simple mathematical treatment the following assumptions are made.

(1) The rate of removal of the gas is proportional both to the concentration of the gas in the stream and to the concentration of " active centres " remaining in the material at any given time. We thus have the relation

$$\partial x/\partial T = kcN$$

where k is a constant, c is the concentration of gas, and N is the number of active centres per c.c. of material.

(2) The active centres do not retain their activity indefinitely. If the gas is being adsorbed, the material becomes saturated with vapour and those parts of the surface which have been " active " become inactive, while if the gas is removed chemically the catalytically active centres become poisoned. We shall assume that, on an average, each active centre deals with n molecules of gas before becoming inactive. If the actual number of active centres per c.c. is N_0', then we may treat these as $nN_0' = N_0$ active centres of unit activity. The factor n is not in practice determinable.

(3) The heat of reaction, or of adsorption, is conducted away immediately.

(4) If local changes of water content of the column occur, they do not alter appreciably the rate of removal of the gas.

In practice the temperature of the adsorbing layer often increases, and breakdown times are dependent on the water content of the material, so that deviations from the theory are most likely to occur when the last two assumptions are unjustified.

Substitution of the above expression for $\partial x/\partial T$ in equation (8) gives

$$-\frac{\partial c}{\partial l} = \frac{1}{L}\left[kcN + \frac{\partial c}{\partial T}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Before proceeding to the general solution of this equation we may first consider conditions under which, contrary to assumption (2) above, the active centres retain their activity indefinitely. N is thus constant and (9) can be solved directly, giving

$$\left.\begin{aligned} c &= c_0\, e^{-kN_0 l/L} \\ \text{or} \qquad \ln c - \ln c_0 &= -kN_0 l/L \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Thus the concentration of the gas falls off exponentially along the column, and the concentration at any point remains constant independent of the time. Hence, if at any given length the concentration is less than the critical concentration for breakdown, the breakdown time for a column of this length is infinity. In practice this ideal case is rarely observed. The solution just obtained, however, arises at zero time when none of the active centres has been used up; the relation (10) is thus the condition which the general solution of (8) must satisfy when T is zero.

The more general case is that in which the active centres are poisoned progressively and the column gradually breaks down. Since each hypothetical active centre, in the sense defined above, deals with one gas molecule and then becomes inactive, the rate of decrease in the number of active centres is equal to the rate of increase in the number of molecules removed from the stream.

Thus

$$-\frac{\partial N}{\partial T} = \frac{\partial x}{\partial T} = kcN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

These simultaneous equations may now be taken with (8) and solved to obtain c as a function of both l and T.* This integration gives the general solution

$$c = \frac{f'(u)}{g(v) + k\,.\,f(u)}$$

where $u = T - l/L$, $v = -l/L$, and $f(u)$ and $g(v)$ are arbitrary functions of u and v respectively. The particular solution required is obtained by introducing the boundary conditions. These are, first, that when $l = 0$, *i.e.*, at the boundary of the column at which the gas enters, the concentration of gas is c_0, and second, that at zero time the concentration falls off exponentially as given by (10).

This leads finally to the relation

$$c = \frac{c_0}{e^{-kc_0 T}\,(e^{kN_0 l/L} - 1) + 1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The concentration of gas escaping through a column of length λ is given by putting $l = \lambda$ in (12). On rearrangement this gives

$$\frac{c_0}{c} - 1 = (e^{kN_0\lambda/L} - 1)\, e^{-kc_0 T} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

so that

$$\ln (c_0/c - 1) = -kc_0 T + \ln (e^{kN_0\lambda/L} - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

In the early stages of breakdown, therefore, when c_0/c is large the graph of $\ln 1/c$ against T should be linear, the slope of the line giving the value of k for the removal of the gas. Later, when c_0/c is not large compared with unity, deviations from this relation are to be expected.

As before, we define the breakdown time, τ, as the time at which the concentration of gas escaping reaches some specified value c'. Putting $c = c'$ and $T = \tau$ in (14) and rearranging, this leads to

$$\tau = \frac{1}{kc_0}\left[\ln (e^{kN_0\lambda/L} - 1) - \ln (c_0/c' - 1)\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

* We are indebted to Dr. J. H. C. Whitehead for the solution.

Effect of Column Length.—Equation (15) can be written in the form

$$\left.\begin{aligned}\tau + \tau_0 &= \frac{1}{kc_0} \ln (e^{kN_0\lambda/L} - 1) \\ \text{where} \qquad \tau_0 &= \frac{1}{kc_0} \ln (c_0/c' - 1)\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots \quad (16)$$

From the values of k and N_0 given later it is seen that we may usually neglect unity in comparison with $e^{kN_0\lambda/L}$ so that we may write

$$\tau + \tau_0 = \frac{N_0}{c_0 L} \cdot \lambda \quad \ldots\ldots\ldots\ldots \quad (17)$$

In this form the equation is more readily interpreted while becoming only slightly less exact.

The graph of breakdown time against column length should be linear, the intercept on the τ axis being $-\tau_0$. Alternatively, on rearrangement,

$$\tau = \frac{N_0}{c_0 L} [\lambda - \lambda_c'] \quad \ldots\ldots\ldots\ldots \quad (18)$$

where λ_c' is the critical length below which the column breaks down immediately and is given by the relation

$$\lambda_c' = \frac{c_0 L}{N_0} \cdot \tau_0 = \frac{L}{kN_0} \ln (c_0/c' - 1) \quad \ldots\ldots\ldots\ldots \quad (19)$$

However, from equation (10), when $T = 0$, the critical concentration is exceeded at all points along the column less than

$$\lambda_c = \frac{L}{N_0 k} \ln c_0/c' \quad \ldots\ldots\ldots\ldots \quad (20)$$

Thus the value of λ_c obtained by extrapolation of the linear portion of the column length–breakdown time curve differs from the true value by the factor

$$\ln (c_0/c' - 1)/\ln c_0/c'.$$

When c_0/c' is large, the difference between the two values of λ_c is negligible, and it follows that the deviation from the linear relation predicted above is also negligible. Thus for most practical purposes we may use equation (17) or (18) in discussing breakdown phenomena.

Effect of Flow-rate.—(a) *If* k *is independent of flow-rate.* (18) and (19) may be rearranged in the form

$$\tau = \frac{N_0\lambda}{c_0} \left(\frac{1}{L} - \frac{1}{L_c}\right) \quad \ldots\ldots\ldots\ldots \quad (21)$$

$$\text{where} \qquad L_c = \frac{N_0 k\lambda}{\ln (c_0/c' - 1)} \quad \ldots\ldots\ldots\ldots \quad (22)$$

Thus a linear relation should exist between the reciprocal of the flow-rate and the breakdown time, and the breakdown time is zero at flow-rates greater than the critical flow-rate L_c.

The critical length and the critical flow-rate are closely related as we see by comparing equations (19) and (22). This may be further illustrated by putting $L = V/A$ in (17), whereupon

$$\tau + \tau_0 = \frac{N_0}{c_0 V} \cdot \lambda A$$

λA is, however, the volume of the column, W, so that

$$\tau + \tau_0 = \frac{N_0}{c_0 V} W \quad \ldots\ldots\ldots\ldots \quad (23)$$

Therefore since τ_0 is independent of L, the breakdown time of a column which has to deal with a volume V of gas per unit time is determined by the total volume of the adsorbent and is not dependent on the ratio of the cross-section of the column to its length. Corresponding to the critical length and the critical flow-rate there is of course a related critical volume.

(b) *If* k *depends on the flow-rate.* The removal of a vapour molecule from the air stream may be regarded formally as taking place in two stages. First, the molecule has to diffuse from the flowing air stream, through a layer of motionless air close to the surface, and secondly, the molecule is adsorbed or converted into products by an action taking place on the surface. The rate of removal will be determined by the slower of the two processes, and for different gases and different materials the rate-determining step is not necessarily the same.

If the rate-determining step is the surface reaction, then the formulæ derived above are valid. On the other hand, if the diffusion process determines the removal rate, then minor modifications have to be made in accordance with the following considerations.

The rate of a heterogeneous reaction governed by a diffusion process is usually given by an equation of the form introduced by Nernst :

$$\frac{dx}{dt} = \frac{DF}{\delta}(c - c^*) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

where D is the coefficient of diffusion of the reacting gas in air, F is the " effective area " of exposed surface, δ is the thickness of the immobile layer, c is the concentration in the air stream, and c^* is the vapour pressure of the gas over the adsorbed surface film. This is essentially the same as equation (11) when c^* is small and F is equated to N_0. The rate constant k is then given by

$$k = D/\delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (25)$$

Experimental evidence indicates that the hypothetical thickness δ depends on the rate of flow of the gas according to an expression of the form

$$\delta = \left(\frac{\delta_r}{L}\right)^n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (26)$$

where δ_r and n are constants : n usually has a value of about $\frac{1}{2}$. Thus if the rate of diffusion governs the adsorption rate we shall expect k to vary with the flow-rate in the following way :

$$k = k_D \,.\, L^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (27)$$

where k_D is proportional to the diffusion constant of the gas in air.

Consequently, we must substitute this expression for k in the equations derived above. This will alter the effect of the flow-rate upon quantities involving k.

Effect of Initial Concentration.—The variation of breakdown time with initial concentration of gas is less easy to express simply. We have, however, that

$$\tau = \frac{1}{kc_0}\left\{\frac{kN_0\lambda}{L} - \ln\frac{c_0}{c'}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (28)$$

so that provided $kN_0\lambda/L \gg \ln c_0/c'$ (*i.e.*, when c_0 is sufficiently small), the breakdown time is inversely proportional to c_0. As c_0 increases, however, the relation deviates steadily from linearity.

Effect of Granule Size.—The above theory applies equally to a column consisting of a single piece of porous material or of a large number of granules. The experiments refer to columns consisting of closely packed granules, and we require to know how the properties of the column depend upon the size of the granules.

The behaviour of each solid–gas system is determined by the two quantities k and N_0. Since k measures the rate of removal of the gas from the air stream, we do not expect it to depend on the size of the granules. Consequently, any changes in the properties of the column with granule size will be due to the effect of granule size on the value of N_0. Now N_0, the " number of active centres " per c.c. of adsorbent, is proportional to the " effective area of exposed surface " in one c.c. of the column, and this in turn depends on the actual surface area of the granules. For a large number of closely packed spheres of equal size, the volume occupied by a given mass is independent of the radius of the spheres provided that the radius remains small compared with the dimensions of the container; the apparent density is independent of the degree of subdivision. The number of particles present in a given volume is, however, inversely proportional to the cube of the radius, while the surface area of each granule is directly proportional to the square of the radius. Consequently, the total surface area of the particles in a given volume will vary inversely with the first power of the radius. If active centres in the core of the particles do not contribute to the adsorptive capacity, then

$$N_0 = Q/d \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (29)$$

where Q is a constant and d is the diameter of the particles.

However, the essential property of an adsorbent is porosity, and the " number of active centres per c.c." is proportional to the *accessible* area. Subdivision results in an increase in the accessible surface which is much less than in proportion to the increase in the area of the formal geometrical boundary of the granule. Further, the accessible area of a given amount of porous material approaches a finite limit as the granule size is reduced and all the pores become accessible from the surface of the granule.

Thus a more rational relation between N_0 and d is of the form

$$N_0 = S \,.\, f(d)$$

where $f(d) \longrightarrow 1$ as $d \longrightarrow 0$ and decreases as d increases; S is the limiting value of N_0 when d is very small.

The exact form of the function is not readily obtained theoretically : we write therefore

$$f(d) = 1 - \alpha d + \beta d^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (30)$$

and determine experimentally the relative importance of successive coefficients. As will be shown, only the first two terms are important, so that

$$N_0 = S(1 - \alpha d) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (31a)$$

The complete breakdown time equation now becomes

$$\tau = \frac{\lambda}{c_0 L} S(1 - \alpha d) - \frac{1}{kc_0} \ln c_0/c' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (31b)$$

and the critical length is given by

$$\lambda_c = \frac{L}{kS(1 - \alpha d)} (\ln c_0/c' - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (31c)$$

Thus decrease in the granule size decreases the critical length and increases the breakdown time. Furthermore, the slope of the column length–breakdown time graph is a linear function of the granule diameter. The value of $-\tau_0$, the intercept of the column length–breakdown time graph on the τ axis is, however, independent of the granule size, so that for a series of similar materials of different granule sizes the column length–breakdown time curves should consist of a pencil of straight lines intersecting on the τ axis at $-\tau_0$.

Distribution of Gas in the Column.—The refinements introduced in the more exact treatment, although giving them a sounder foundation, do not result in any important modifications in the breakdown formulæ; the limitations of the approximate treatment become apparent, however, when we consider the distribution of the vapour both in the gaseous phase and on the solid in the column.

(a) *In the gas phase.* The distribution in the gas phase at various distances along the column is given at time T by equation (12) which may be written in the form

$$\ln (c_0/c - 1) = \ln (e^{kN_0 l/L} - 1) - kc_0 T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (32)$$

When l is large and c is small then

$$\ln c_0/c = \frac{kN_0 l}{L} - kc_0 T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (33)$$

The graph of $\ln c$ against l should then be a straight line of slope kN_0/L. At smaller distances along the column, deviations from this simple form [which also follows directly from equation (4) of the approximate treatment] become large.

(b) *On the solid.* The way in which we have defined an " active centre " is such that the amount of gas which has been adsorbed on or removed by a given element of material is equal to the number of active centres which have been exhausted. The concentration of active centres left at time T, at a distance l along the column is given by

$$N_{l,T} = N_0 - x_{l,T} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (34)$$

where $x_{l,T}$ is the concentration of adsorbed gas or reaction product per c.c. of material at this point. Taking this equation with (11) and (12), we have

$$\frac{dx}{dT} = \frac{kc_0(N_0 - x)}{[e^{-kc_0 T} (e^{kN_0 l/L} - 1) + 1]}$$

Thus

$$\int_0^x \frac{dx}{N_0 - x} = \int_0^T \frac{kc_0 dT}{[e^{-kc_0 T} (e^{kN_0 l/L} - 1) + 1]}$$

Integration of this gives

$$\ln \frac{N_0}{N_0 - x} = \ln [e^{-kN_0 l/L} (e^{kc_0 T} - 1) + 1]$$

This can be rearranged to give

$$\ln \frac{x}{N_0 - x} = -\frac{kN_0 l}{L} + \ln (e^{kc_0 T} - 1)$$

or approximately, when T is large,

$$\ln \frac{x}{N_0 - x} = -\frac{kN_0 l}{L} + kc_0 T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (35)$$

Thus at a given time, $\ln x/(N_0 - x)$ should fall off linearly with l, while at a given distance along the column, it should increase approximately linearly with the time. Alternatively, we can rearrange (35) to give

$$\frac{x}{N_0} = \frac{c}{c_0} (1 - e^{-kc_0 T}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (36)$$

which shows that at a given time the concentration of gas or product which has accumulated is proportional to the concentration of gas in the gas phase at the same distance along the column.

Total Amount of Gas Penetrating the Column.—The breakdown time of a column has been defined as the time at which the concentration of escaping gas exceeds an arbitrarily chosen value c'. Experimentally, however, it is often more convenient to determine the time at which the *total amount* of gas which has penetrated the column reaches a certain value γ'. The equations obtained above correspond to the first definition. It is

of interest, therefore, to consider the equations obtained when the breakdown time is defined by the latter criterion.

The total amount of gas escaping through the column in a time T is given by

$$\gamma = L\int_0^T c \,.\, \mathrm{d}T \text{ per unit cross section.}$$

Substituting for c from (12), we obtain

$$\tau_{\gamma'} = \frac{1}{kc_0} \ln \left[e^{kN_0\lambda/L}\left(e^{k\gamma'/L} - 1\right) + 1\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (37)$$

It may be noticed that, whereas the condition for the approximation made in passing from (16) to (17) is

$$e^{kN_0\lambda/L} \gg 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

yet in the present case the corresponding one would be

$$e^{kN_0\lambda/L}\left(e^{k\gamma'/L} - 1\right) \gg 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

It is easily shown that corresponding to the usual breakdown criteria $e^{k\gamma'/L} - 1 < 1$, so that condition (ii) holds less exactly than (i) at a given column length. Consequently, on decreasing λ or increasing L, deviations from the simple linear relations should appear sooner if we take the γ' criterion instead of the c' criterion of breakdown.

Comparing (15) with (37), we see that the form of the breakdown equation is not altered by changing the criterion of breakdown. The slope of the column length–breakdown time curve is the same but the intercept on the τ axis is now given by

$$(\tau_0)_{\gamma'} = \frac{1}{kc_0} \ln \left(e^{k\gamma'/L} - 1\right)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (38)$$

instead of by

$$(\tau_0)_{c'} = \frac{1}{kc_0} \ln \left(c_0/c' - 1\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

Similarly, in the other formulæ $(e^{k\gamma'/L} - 1)^{-1}$ occurs in place of $c_0/c' - 1$. The two criteria of breakdown thus become identical if we choose γ' and c' so that

$$(c_0/c' - 1)(e^{k\gamma'/L} - 1) = 1$$

i.e.,

$$c'/c_0 = 1 - e^{-k\gamma'/L} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (39)$$

Thus if we determine the value of c' which corresponds to a chosen breakdown criterion γ' for a given material at a certain flow-rate, then γ' will correspond to a different value of c' if we change the flow-rate or use another material for which the value of k is different.

The effect of changing L on the value of $(\tau_0)_{\gamma'}$, as compared with $(\tau_0)_{c'}$ is seen by the following rough calculation.

If under given conditions γ' corresponds to $c'/c_0 = 0{\cdot}01$, then $e^{k\gamma'/L} - 1$ has the value of 0·01 also, and $\ln (e^{k\gamma'/L} - 1)^{-1} = 4{\cdot}6$. If the value of L is doubled, this value changes by 0·7 approximately, *i.e.*, by about 15%; $(\tau_0)_{c'}$ is unchanged by the change in L (if k is independent of L). A change of 15% in the value of τ_0 corresponds to a change of not usually more than 10% of the breakdown time for a 6-cm. column. Similar considerations apply to the effect of change in k, and it is seen that no very serious differences will be likely to occur in practice if we find it more convenient to use the γ' criterion rather than the c' criterion.

Survey of Experimental Results.

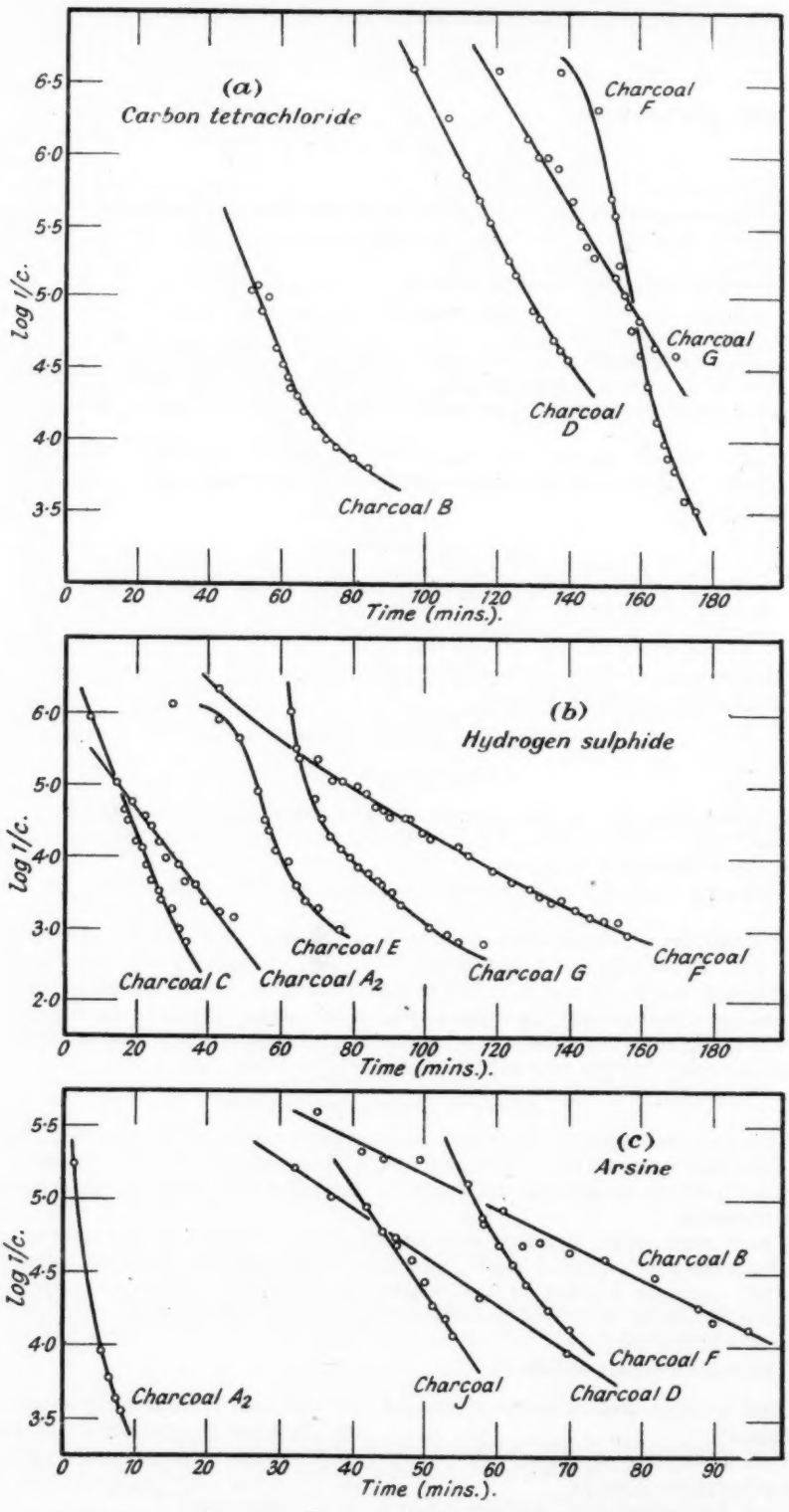
In this section are collected together a representative series of experimental results to illustrate the formulæ above. The material used was granular active charcoal, and the uptake of various gases by this was studied. No attempt has been made to present all the available data, but only sufficient to demonstrate the general validity of the relationships.

The charcoals used were either standard commercial active carbons or charcoals of increased catalytic activity prepared from them by chemical impregnation in the laboratory. Similarly named charcoals are not necessarily identical; separate batches of the small-scale laboratory preparations vary somewhat among themselves. There is, however, no reason to believe that any important difference in behaviour is shown by different charcoals of a given type.

Details of the charcoals used are as follows :

A.1 Steam activated coconut-shell charcoal of low adsorptive capacity.
A.2 ditto, medium adsorptive capacity.
A.3 ditto, high adsorptive capacity.
B Steam-activated, briquetted coal, medium adsorptive capacity.
C Charcoal A.2 impregnated with silver nitrate.
D Charcoal B, containing copper.
E Charcoal B, containing CuO and MnO_2.
F Charcoal B, impregnated with iodic acid.
G Charcoal B, impregnated with ammonium vanadate.
H Charcoal A.2 containing copper.
J Charcoal A.2 impregnated with iodic acid.

FIG. 1.



Variation of $\log\left(\frac{1}{\text{escaping concentration}}\right)$ *with time for various charcoals :*
(a) *carbon tetrachloride,* (b) *hydrogen sulphide,* (c) *arsine.*

All the charcoals were tested when containing 16% of moisture. Except where otherwise stated they were in the form of granules graded between 8 and 18 B.S.S. sieve sizes.

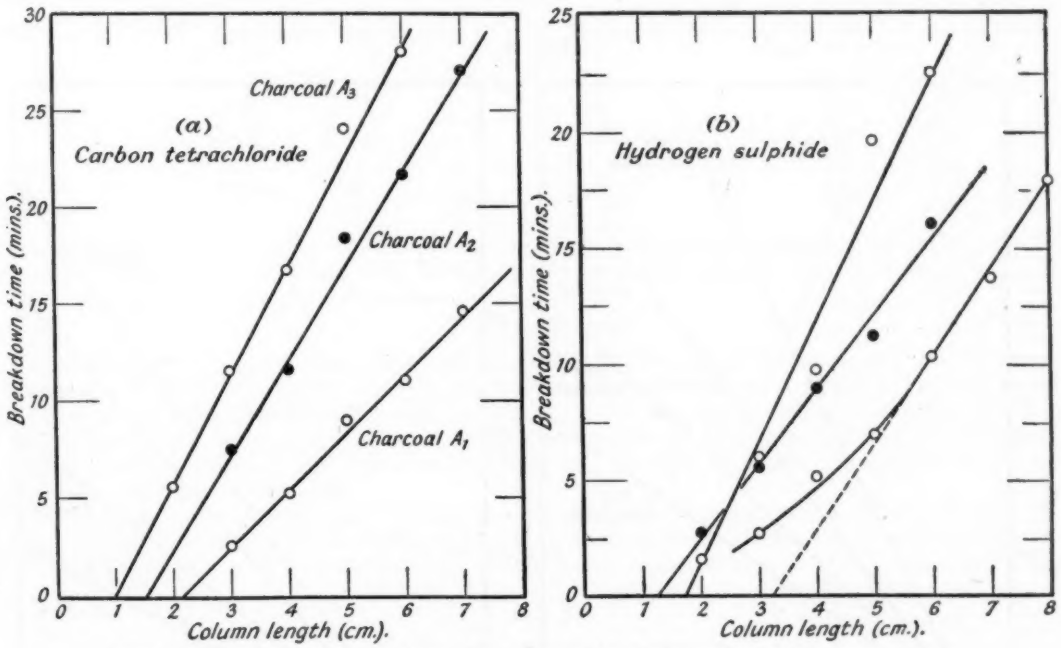
In all experiments columns of charcoal 1 cm. in diameter were used. The column length was 6 cm., and the flow-rate of the air stream 200 c.c./min., except where the effect of variation in these quantities was being investigated.

Many gases were used but the results given below refer mainly to arsine, hydrogen sulphide, and carbon tetrachloride. Of these the first two satisfy the condition of being irreversibly destroyed on active charcoal (by oxidation).

Relation between Escaping Concentration and Time.—Equation (14) predicts that on plotting the logarithm of the concentration of gas escaping from the column against the time a straight line should be obtained. Results are shown graphically in Figs. 1(*a*), 1(*b*) and 1(*c*).

In general, the linear relationship is followed over an appreciable range of concentration. At higher concentrations we expect deviations from linearity, while at low concentrations experimental difficulties

FIG. 2.



Effect of column length on breakdown time : (a) *carbon tetrachloride,* (b) *hydrogen sulphide.*

make the exact determination of the curves difficult. The slope of each of these lines gives the value of kc_0 and hence k for each gas–charcoal combination.

Effect of Column Length.—In Figs 2(*a*) and 2(*b*) are plotted results for the effect of column length on the breakdown of several charcoals towards two typical gases. In general, the linear relation predicted between the breakdown time and the column length is well obeyed. The values of the critical column length under which breakdown, under the conditions used, is instantaneous are seen to vary from about 1 cm. to 3 cm. N_0, the concentration of active centres, may be calculated from the slope of the column length–breakdown time curves.

Effect of Flow-rate.—According to equation (21) a linear relation should exist between the breakdown time and the reciprocal of the flow-rate, the intercept on the $1/L$ axis giving the value of the critical flow-rate above which the column of charcoal breaks down instantaneously. The flow-rate and the column length effects are closely related, and change in flow-rate alters the critical length and the slope of the column length–breakdown time curves.

Table I contains the results of experiments in which both column length and flow-rates were varied.

The breakdown of the charcoal was followed over a range of escaping concentrations and the rate constant k evaluated (Table II, col. 2). It is seen that this constant depends on the flow-rate, and in col. 6 the approximate constancy of $k/L^{\frac{1}{2}}$ suggests that we are dealing with a process governed by the rate of diffusion of the vapour.

In Fig. 3(*a*) are plotted the column length–breakdown time curves at different flow-rates. The intercepts λ_c and τ_0 depend on the flow-rates. λ_c is proportional, and τ_0 inversely proportional, to $L^{\frac{1}{2}}$ as shown in cols. 7 and 8 of the table. The slope of the lines $(d\tau/d\lambda)$ is inversely proportional to L (col. 9).

The relation between τ and $1/L$ is shown in Fig. 3(*b*). The critical flow-rate appears to vary with column length as indicated by equation (22). The results are not sufficiently accurate, however, to provide more than a qualitative verification of the relation.

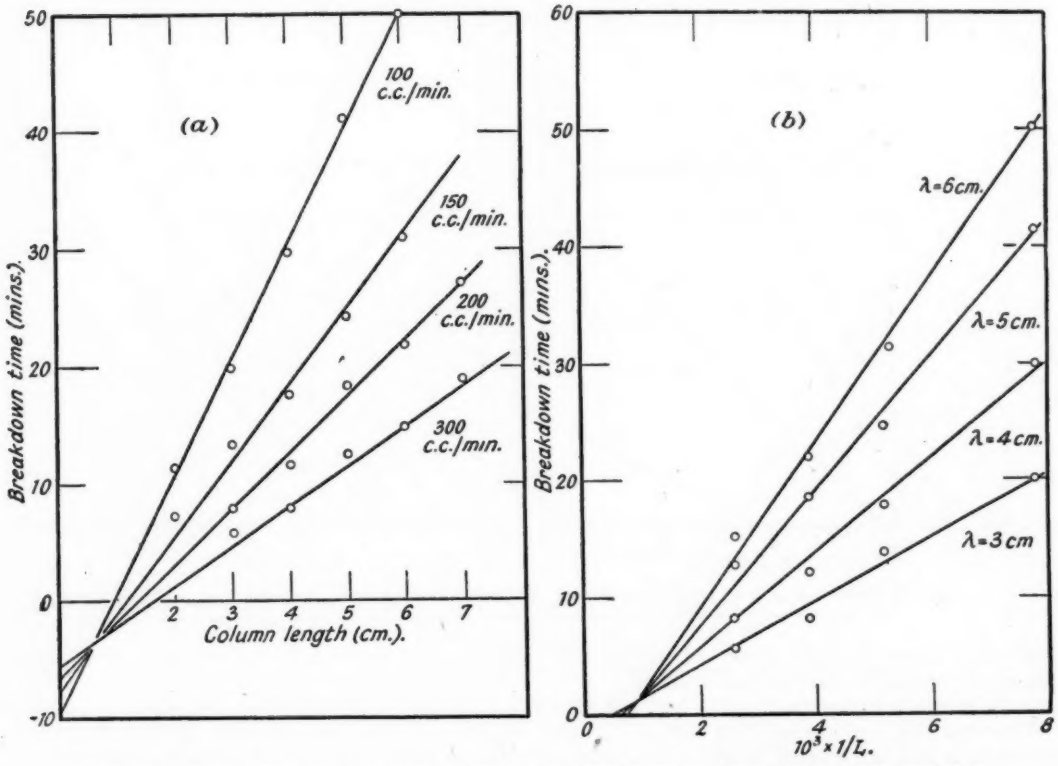
TABLE I.

Charcoal A.2, graded 10—12 B.S.S.

Carbon tetrachloride, $c_0 = 2{\cdot}16\%$.

L = 128 cm./min.			L = 192 cm./min.			L = 256 cm./min.			L = 384 cm./min.		
λ.	τ.	$\frac{kc_0}{2{\cdot}3}$.	λ.	τ.	$\frac{kc_0}{2{\cdot}3}$.	λ.	τ.	$\frac{kc_0}{2{\cdot}3}$.	λ.	τ.	$\frac{kc_0}{2{\cdot}3}$.
2·0	11′ 28″	0·30	2·0	7′ 10″	0·24	3·0	7′ 40″	—	3·1	5′ 45″	0·41
3·0	19 47	0·24	3·0	13 30	0·31	4·0	11 35	—	4·0	7 47	0·39
4·0	29 41	0·24	4·0	17 29	0·35	5·0	18 20	—	5·0	12 28	0·34
5·0	42 12	0·22	5·0	24 13	0·32	6·0	21 40	0·34	6·0	14 47	0·37
6·0	51 25	0·25	6·0	30 56	0·37	7·0	27 00	—	7·0	18 50	0·38
	Mean	0·25		Mean	0·32		Mean	0·34		Mean	0·38

FIG. 3.



Effect of column length and flow-rate on breakdown time for carbon tetrachloride : Charcoal A.2.

The relationship between the breakdown time and the total volume of charcoal, as expressed by (23), may also be illustrated. Table III gives the values of λ required to obtain a predetermined breakdown time at different flow-rates. The ratio of the column length to the flow-rate is given, and in the last column are the volumes of charcoal required to give the stated breakdown times.

It is seen that for arsine and hydrogen sulphide the volumes required are independent of the flow-rate. For carbon tetrachloride and ammonia there is a slight increase in the requisite volume for low flow-rates,

TABLE II.

L.	k.	λ_c.	τ_0.	$d\tau/d\lambda$.	$k/L^{\frac{1}{2}}$.	$\lambda_c/L^{\frac{1}{2}}$.	$\tau_0 L^{\frac{1}{2}}$.	$L(d\tau/d\lambda)$.
128	600	0·95	9·5	10·0	53	8·4	108	1280
192	760	1·15	7·5	6·3	56	8·4	103	1220
256	810	1·30	6·3	4·7	51	8·2	101	1200
384	910	1·60	5·5	3·4	47	8·2	108	1300

corresponding to a short, wide column. This effect may be accounted for by the dependence of k on the flow-rate for these two gases.

TABLE III.

Total flow, 16 *litres/min.*

L, c.c./sq. cm. per min.	A, sq. cm.	W, c.c. Charcoal A.2, 10—12 B.S.S.	Charcoal A.3, 10—12 B.S.S.	Charcoal B, 10—12 B.S.S.
Carbon tetrachloride, $c_0 = 2{\cdot}16\%$. Required breakdown time, 26 mins.				
128	125	450	—	—
192	83·5	435	335	490
255	62·5	430	315	445
320	50·0	—	300	410
384	41·5	390	—	—

L, c.c./sq. cm. per min.	A, sq. cm.	W, c.c. Charcoal B, 14—16 B.S.S.	Charcoal F, 10—12 B.S.S.	Charcoal D, 10—12 B.S.S.
Arsine, $c_0 = 0{\cdot}50\%$. Required breakdown time, 75 mins.				
192	83·5	440	465	455
255	62·5	450	430	455
320	50·0	455	500	430

Ammonia, $c_0 = 1{\cdot}00\%$. Required breakdown time, 40 mins.				
		Charcoal A.3, 10—12 B.S.S.	Charcoal A.3, 16—18 B.S.S.	Charcoal C, 7—18 B.S.S.
192	83·5	960	810	775
255	62·5	940	750	640
320	50·0	925	700	630

Hydrogen sulphide, $c_0 = 2{\cdot}56\%$. Required breakdown time, 23 mins.			
		Charcoal B, 12—14 B.S.S.	Charcoal D, 10—12 B.S.S.
192	83·5	415	375
255	62·5	415	375
320	50·0	420	350

Effect of Initial Concentration.—The results of a series of experiments on the effect of initial concentration on breakdown times are given in Fig. 4(*a*), where τ is plotted against $1/c_0$ for a series of gases and charcoals. The existence of a critical initial concentration given by

$$(c_0)_c = c' e^{kN_0 A/L}$$

above which the breakdown of a 6-cm. column is instantaneous is illustrated by the results for arsine on charcoal C and hydrogen sulphide on charcoal A.2. In the other cases shown the critical initial concentrations are very large so that the lines pass practically through the origin. In all cases these critical values are greater than 5%. Fig. 4(*b*) contains the same results, but here $1/\tau$ is plotted against c_0. It is seen that a pencil of lines through the origin is obtained, and that as c_0 increases deviations from linearity occur, the charcoal becoming relatively *less* efficient at higher concentrations.

The deviations from linearity are in the direction to be expected theoretically. The behaviour may, however, be complicated by temperature changes in the charcoal column. With high concentrations the temperature and the efficiency of the column will be considerably higher than with low, and this effect will tend

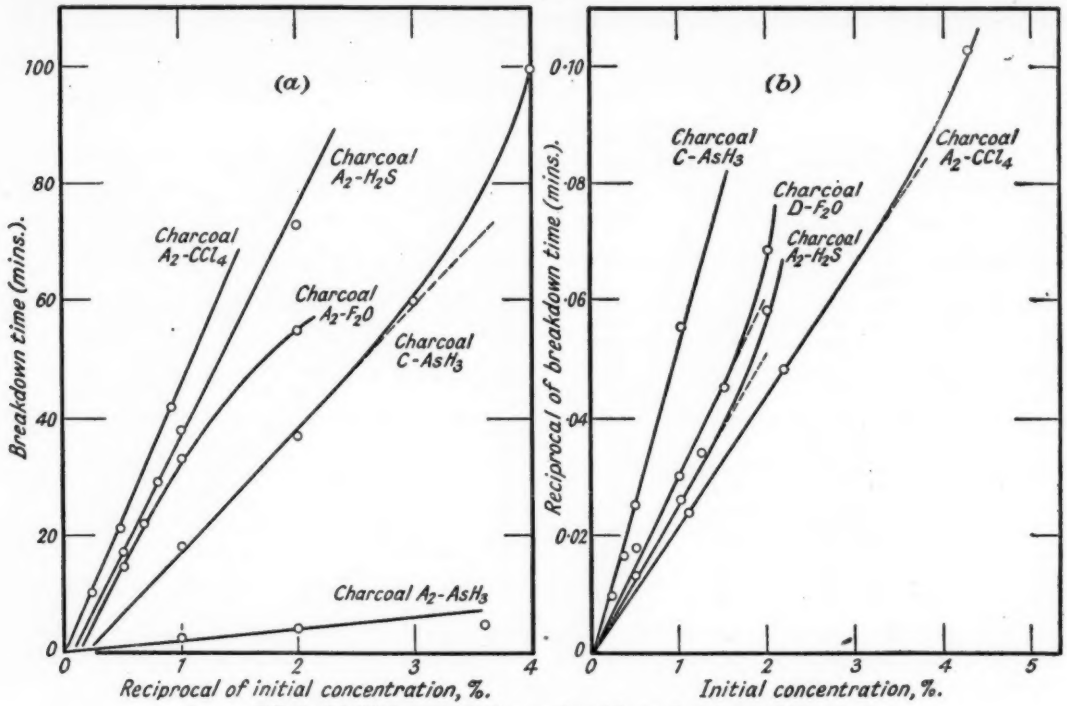
TABLE IV.

	Carbon tetrachloride. Charcoal A.2. $c_0 = 1{\cdot}08\%$.	2·16%.	3·34%.
λ.	τ.	τ.	τ.
2·0	8′ 47″	—	—
3·0	17 47	7′ 40″	—
4·0	—	11 35	8′ 35″
4·5	29 08	—	—
5·0	—	18 20	11 36
6·0	40 50	21 40	15 44
7·0	—	27 00	19 05
8·0	—	—	24 14
$d\tau/d\lambda$, mins./cm.	8·5	4·8	3·4
λ_c, cm.	0·9	1·4	1·6
τ_0, mins.	8·0	4·7	3·4
$c_0\,(d\tau/d\lambda)$	9·2	10·4	10·9

to operate in the opposite sense. Thus we may expect to find in different cases deviations from linearity in both senses. For practical purposes, however, we may regard $1/\tau$ as directly proportional to c_0 for small initial concentrations.

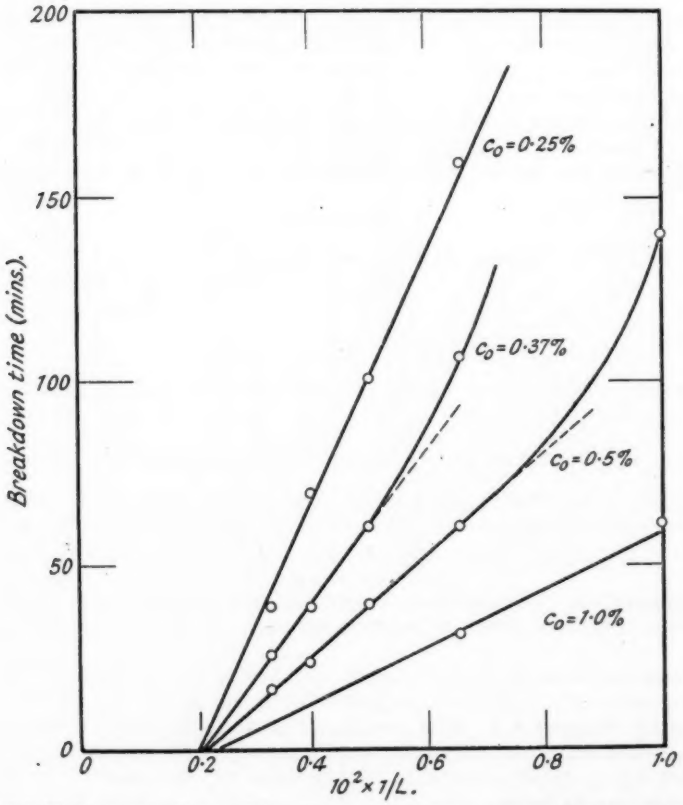
Effect of Initial Concentration on the Critical Length and the Critical Flow-rate.—The influence of the initial concentration on the variation of breakdown time with column length has been investigated for the adsorption of carbon tetrachloride by charcoal A.2. The results are given in Table IV. The critical length decreases with the initial concentration and, over the rather small range studied, equation (19), which predicts a linear relation between λ_c and log c_0, appears to hold. The inverse proportionality between $d\tau/d\lambda$ and c_0 is also confirmed within the experimental error.

FIG. 4.



Effect of initial concentration on breakdown time for various gases.

FIG. 5.



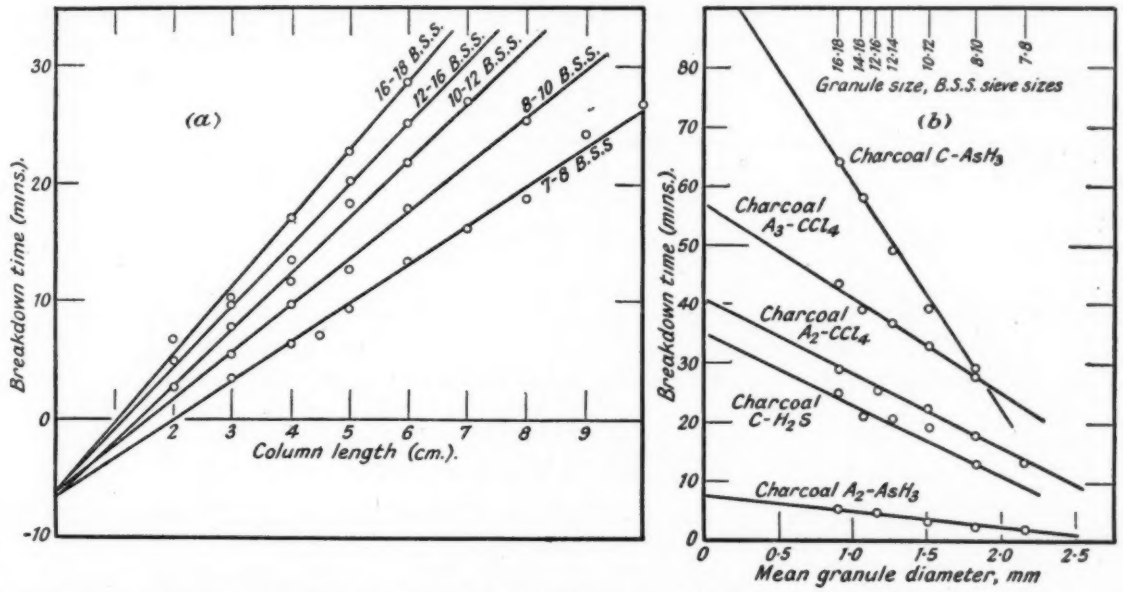
Effect of initial concentration and flow-rate on breakdown time for arsine: Charcoal C.

The variation of breakdown time with flow-rate has been studied at several different initial concentrations in the removal of arsine by charcoal C. The results are shown in Fig. 5, where the breakdown times are plotted against the reciprocal of the flow-rate : $1/L_c$ is found to vary linearly with $\log c_0$ (equation 22) ; a 10-fold change in c_0 (from 1% to 0·1%) only increases the critical flow-rate from 600 to 850 cm./min. The slopes of the lines in Fig. 5 are proportional to $1/c_0$.

Effect of Granule Size.—If k is independent of granule size, equation (17) predicts that the column length–breakdown time curves for charcoals differing only in their granule sizes should consist of a pencil of lines intersecting on the τ axis at $-\tau_0$. Furthermore, the variation of the slopes of these lines with granule diameter will give the relation between N_0 and granule size.

Typical results are plotted in Fig. 6(*a*). The intercept on the τ axis of the graphs of τ against λ is nearly

FIG. 6.



Effect of granule size on breakdown time : (a) *Column length–breakdown time relation for various granule sizes : carbon tetrachloride–charcoal A.2.* (b) *Relation between granule size and breakdown time for various gas–charcoal systems at constant column length* (6 *cm.*).

constant, thus confirming that k is independent of the granule size. On plotting the values of $d\tau/d\lambda$ against the mean granule size, linear graphs are obtained, showing that N_0 is of the form

$$N_0 = S(1 - \alpha d) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (31a)$$

Equation (29) is thus shown to be invalid, and the coefficient of d^2 in equation (30) is negligible. In Fig. 6(*b*), τ is plotted against mean granule size for a series of gas–charcoal systems; these results confirm equation 31(*b*).

The above equation has been found to represent the effect of granule size for a large number of gas–charcoal pairs, the value of α for all these being $0{\cdot}26 \pm 0{\cdot}04$ when d is expressed in mm.

Distribution of Gas in the Column.—The simple treatment of the theory of breakdown gives no indication of the amount of gas dealt with by successive layers of charcoal as the deactivating wave proceeds along the column. The more complete treatment leads to equations giving the form of the distribution curves of gas held on the charcoal and of gas remaining in the air stream (equations 32 and 35). These equations should hold for systems in which the gas is removed irreversibly (*e.g.*, by chemical reaction), but they will be in error if appreciable desorption of the gas takes place. The amount of gas held by the charcoal at any point will then be less than that predicted by equation (35), the discrepancy increasing with the amount held.

The experiments described below illustrate the behaviour of two typical gases, *viz.*, arsine, which is irreversibly destroyed, and hydrogen cyanide, for which the desorption is considerable.

The distribution of arsine on the charcoal at various points in the column was investigated by direct analysis of small sections, preliminary experiments having shown that arsine is oxidised to a mixture of arsenate and arsenite on the charcoal surface.

Five sections of charcoal C, each weighing 0·7 g., were packed into the testing tube, the sections being separated by small cotton-wool pads. The arsine–air stream was passed for a given time, and the arsenic in each section was determined by extraction with hot alkali, reduction of the acidified extract with sulphur

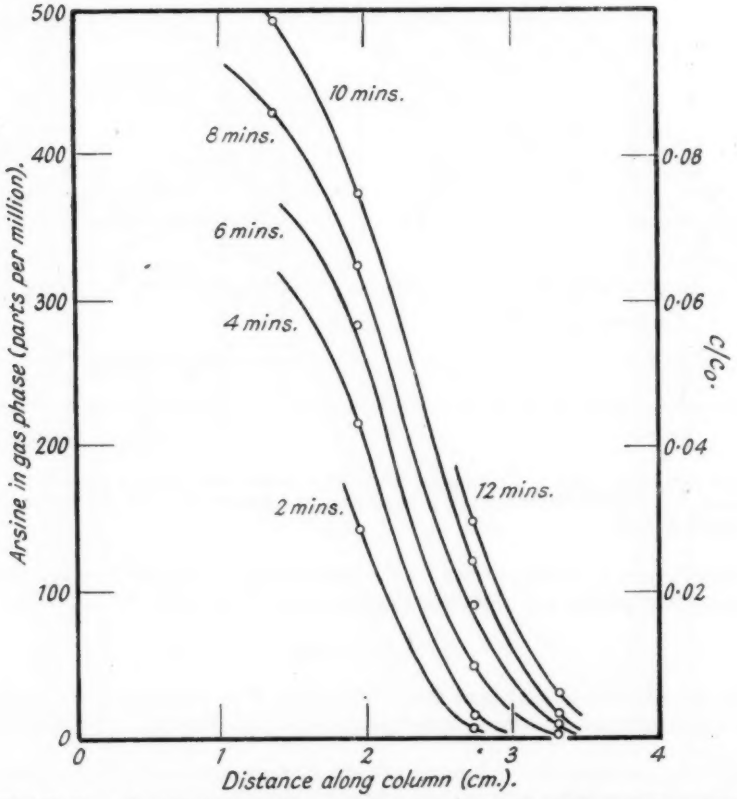
dioxide, removal of excess sulphur dioxide, and titration of the neutralised sample with standard iodine. The results are contained in Table V.

TABLE V.

Time of passage of stream.	30′.	63′. (Breakdown.)	120′.
	Number of c.c. of AsH_3 dealt with by each section.		
1st Section	19·9	33·2	43·0
2nd „	10·7	24·4	37·8
3rd „	1·9	13·9	26·8
4th „	0·3	3·0	21·0
5th „	0·1	0·4	8·0

In Fig. 8(*a*), $\log x/(N_0 - x)$ is plotted against the column length at three different times; approximately linear graphs are obtained of approximately the same slope. In this example equation (35) seems to be followed closely.

FIG. 7.



Distribution of arsine in gas phase along column during breakdown (Charcoal C).

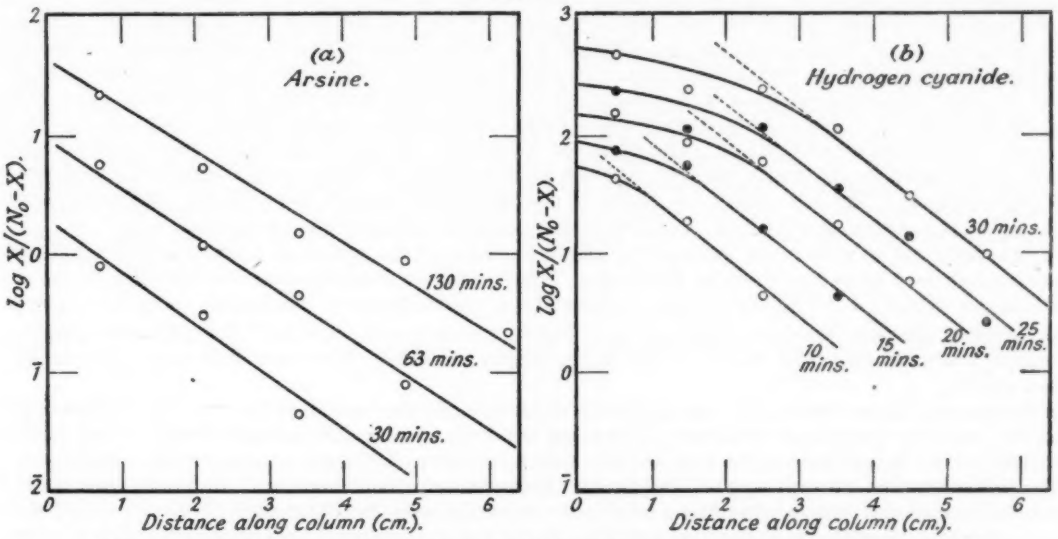
To investigate the concentration of arsine in the gas phase at various points in the column during the initial stages, concentration–time curves for various column lengths of charcoal C were obtained. From these curves the concentrations leaking through at various times at different column lengths were read off. These concentrations were then plotted against the respective column lengths, giving the concentration gradients at various times (Fig. 7). The curves give a fair idea of how the concentration gradient moves along the column.

Similar experiments were made with hydrogen cyanide by a method to be described in detail in a later paper. The relation between $\log x/(N_0 - x)$ and l for this system [Fig. 8(*b*)] is seen to depart from linearity as the amount of gas on the charcoal increases; the deviation is in the direction expected. The theory developed in this paper is, in fact, inadequate to predict the distribution curves for gases reversibly adsorbed on charcoal. A treatment of this problem is attempted in a later paper.

Discussion of k *and* N_0.—Table VI gives the experimentally determined values of k, N_0, and S for various gas–charcoal combinations. k has been determined either directly from the slope of the curves of $\log 1/c$ against time or from the intercept on the τ axis of the curves of column length against breakdown time: the

units are (g.-mol./l.)$^{-1}$(min.)$^{-1}$. Where direct comparison between values of k evaluated by the two methods is available, there is moderate agreement except for some results with arsine; the figures given are mean values. N_0 has been calculated from the slope of the column length–breakdown time graphs and is expressed in terms of the number of " active centres " of unit activity per c.c. of packed granular charcoal and refers to a standard

FIG. 8.



Distribution of adsorbed gas along column during breakdown : (a) *arsine,* (b) *hydrogen cyanide.*

TABLE VI.

Values of k, N_0, S, *and* α.

Charcoal.	k.	$N_0 \times 10^{20}$.	$S \times 10^{20}$.	α.	Mean k.	$k\sqrt{VD}$.
Carbon tetrachloride.						
A.1	760	4·5	—	—		
A.2	755	7·2	11·3	−0·26		
A.3	870	8·7	16·5	−0·26	700	6100
B	660	—	—	—		
D	600	—	—	—		
Ammonia.						
A.3	2240	2·0	3·2	−0·23	2020	5760
C	1800	2·5	4·4	−0·28		
Hydrogen cyanide.						
A.3	1600	3·5	6·3	−0·29	1600	5900
C	1600	4·2	8·1	−0·29		
Chloropicrin.						
A.2	615	—	—	—		
A.3	589	11·0	18·5	−0·24	620	5600
B	670	—	—	—		
Arsine.						
A.2	4000	0·7	—	—		
B	240	—	—	—		
C	500	4·6	7·0	−0·28		
D	430	7·2	11·5	−0·28	—	—
E	780	6·0	—	—		
F	600	5·7	—	—		
H	550	6·4	—	—		
J	820	—	—	—		
Hydrogen sulphide.						
A.2	475	7·0	—	—		
C	510	8·8	12·0	−0·24		
D	—	9·4	14·0	−0·21	—	—
E	450	5·6	—	—		
F	183	9·0	—	—		
J	146	—	—	—		

spectrum of granule sizes in the range 8—18 B.S.S. sieve sizes; S is the limiting value of N_0 when the granule size is indefinitely small.

It is immediately apparent that k and N_0 (or S) are quite independent properties of a gas–charcoal system, high values of N_0 being accompanied by both small and large values of k.

The Rate Constant, k.—The rate of removal of the gas may be determined either by the rate of diffusion to the surface, or by the rate of the process which occurs at the surface, whichever is the slower.

If diffusion determines the overall rate, then a dependence of k on the flow-rate is predicted. The experimental results in Table II show that for the adsorption of carbon tetrachloride k is proportional to the square-root of the flow-rate; similar, though less extensive, results are also available for ammonia, hydrogen cyanide, and chloropicrin. Further evidence that diffusion is the rate-determining step in these cases is provided by the figures in Table VI. For the above-mentioned gases k is the same for the various charcoals, and is determined only by the nature of the gas. The observed values of k should be proportional to the diffusion coefficients of the gases in air, which we may suppose to be roughly inversely proportional to the square-roots of the gas densities. The last column of Table VI shows that for carbon tetrachloride, ammonia, hydrogen cyanide, and chloropicrin, the product $k\sqrt{VD}$ is in fact constant within the experimental error.

For the oxidation of arsine and hydrogen sulphide on charcoal the values of k are practically independent of flow-rate but vary from one charcoal to another. This suggests that the chemical reaction on the surface determines the value of k. This view is strengthened by a consideration of the magnitude of k to be expected for these gases if diffusion were rate-determining. Taking the mean value of $k\sqrt{VD}$ for the adsorbable gases, we calculate $k = 1000$ for arsine and $k = 1530$ for hydrogen sulphide. These are both much greater than the observed values.

The Number of Active Centres, N_0.—As originally defined, N_0 is the total number of accessible active points, each of unit activity, per c.c. of charcoal. For gases removed by chemical reaction this quantity is directly proportional to the actual number of catalytically active centres. If the gas is removed by adsorption, however, the present treatment only applies strictly to " breakdown " phenomena and cannot account accurately for the behaviour of the system when the partial pressure of gas over the charcoal is high. We shall thus not expect to correlate N_0 with the saturation capacity of the gas under static conditions. N_0 will be rather the number of *possible* sites on which the gas could be adsorbed; at equilibrium only a fraction of these need be occupied. In this way N_0 will determine the rate of adsorption when the reverse process is negligible.

The absolute magnitude of N_0 for all the gases is of the order 10^{21}. The total number of carbon atoms in one c.c. of granulated charcoal is roughly 3×10^{22}, so that a high degree of availability of the carbon atoms in a granule is indicated.

The variation of N_0 with granule size, for nine gas–charcoal systems examined, follows with fair accuracy the relation $N_0 = S(1 - 0{\cdot}26d)$. The coefficient 0·26 measures the way in which additional pores of the charcoal structure become available as the granule size is reduced. No simple geometrical interpretation of the expression has, however, been found.

For a given charcoal, the value of S varies with the gas. For adsorbed gases S increases with the molecular weight, the magnitude of the effect being itself dependent upon the charcoal.

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PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, February 13th*, 1946.]

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203. 4-n-*Propyl-picolinic and -pipecolinic Acids. Limitations of the Wibaut–Arens Reaction with α-Substituted Pyridine Derivatives.*

By W. SOLOMON.

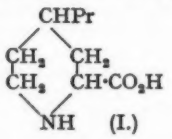
The preparation is described of 4-n-*propylpicolinic acid* (II) from 4-*n*-propylpyridine in four stages. It furnishes on reduction 4-n-*propylpipecolinic acid* (I). The failure is recorded of attempts to introduce the *n*-propyl group by the Wilbaut–Arens reaction (*Rec. Trav. chim.*, 1941, **60**, 119; 1942, **61**, 59) into the 4-position of the pyridine nucleus of eight α-substituted pyridine derivatives, thus pointing to the generalisation that α-substituted pyridine derivatives, unlike pyridine itself, cannot be alkylated by this method.

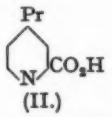
IN the course of work proceeding in these laboratories it became necessary to obtain 4-n-*propylpipecolinic acid* (I). The most attractive method appeared to be the introduction of the propyl group into the 4-position of the pyridine nucleus in picolinic acid (III; R = CO_2H) using the Wibaut–Arens reaction (*loc. cit.*), followed by the reduction of the resulting acid (II). As this proved unsuccessful, attention was next turned to the possibility of introducing the propyl group into other α-substituted pyridine derivatives (III) in which R might be a group subsequently convertible into carboxyl.

Apart from picolinic acid itself (III; R = CO_2H) seven other substances were tried, namely (III; R = Me, CO_2Et, $CO{\cdot}NH_2$, CN, CH:CHPh, NH_2, and Cl), but in no case could a propyl derivative of the starting material be isolated from the products of the reaction.

The Wibaut–Arens reaction (compare *Ann. Reports*, 1941, **38**, 223; 1943, **40**, 163) is based on an original

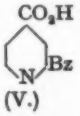
observation of Dohrn and Horsters (G.P. 390,333/1922; *Chem. Zentr.*, 1924, ii, 891) that pyridine and α-picoline on treatment with zinc dust and acetic anhydride are converted in fair yield into the respective 4-ethyl derivatives. The Dutch workers showed that analogous reactions occurred with other fatty acid anhydrides, and thus added a new, valuable method to the few unsatisfactory ones hitherto available for the preparation of 4-alkylpyridine derivatives; however, they restricted their study to unsubstituted pyridine itself. On the other hand, Dohrn and Horsters (*loc. cit.*) not only describe the preparation of 2-methyl-4-ethylpyridine from α-picoline as already stated, but lay general claim to the applicability of the reaction to " pyridine homologues." In view of the present author's results with eight α-substituted pyridine derivatives (including α-picoline) using propionic anhydride, the German claim that α-picoline could be converted into 2-methyl-4-ethylpyridine was re-examined by causing α-picoline to react with zinc dust and acetic anhydride under a variety of conditions, which included (*a*) those described in the patent, (*b*) those worked out by Wibaut and Arens for pyridine and acetic anhydride, as well as (*c*) other variations devised by the author. In no case could the desired product be isolated. More than half the picoline remained unchanged, while the greater part of the remainder became converted into high-boiling or even non-volatile, viscous material. Essentially similar results were obtained in the series of eight experiments with propionic anhydride already mentioned.


(I.)


(II.)

(III.)

(IV.)


(V.)

2-Aminopyridine (III; R = NH_2) was exceptional in its inertness, the only observable reaction being propionation: on hydrolysis the substance was recovered unchanged in almost quantitative yield. α-Stilbazole (III; R = CH:CHPh) underwent some reduction to the known 2-2′-phenylethylpyridine (III; R = CH_2·CH_2Ph), while 2-chloropyridine (III; R = Cl) suffered some dehalogenation. Most of the reaction mixtures were complex and it cannot be asserted that none contained any of the desired product, only that none could be isolated. It seems therefore that the patent claim is unfounded, its specific example irreproducible, and that, unlike pyridine itself, α-substituted pyridine derivatives cannot successfully be alkylated in the 4-position by means of the Wibaut–Arens reaction.

Other attempts to prepare 4-propylpicolinic acid by direct methods included some experiments on the introduction of suitable hydrocarbon residues into the 2-position in 4-propylpyridine either by means of Grignard reagents and lithium compounds, or directly. The styryl radical could not be introduced, but *2-benzyl-4-n-propylpyridine* (IV; R = CH_2Ph) was prepared by the direct interaction of 4-propylpyridine with benzyl chloride in the presence of copper-bronze at 250° (cf. Maier-Bode and Altpeter, " Das Pyridin und seine Derivate," Wilhelm Knapp, 1934, p. 39). However, on oxidation with permanganate in hot aqueous acid solution, this furnished 2-*benzoylisonicotinic* acid (V).

4-Propylpicolinic acid was finally obtained in orthodox fashion by a longer route from 4-propylpyridine. The latter, prepared from pyridine, propionic anhydride, propionic acid, and zinc dust by the method of Arens and Wibaut (*loc. cit.*), gave with sodamide the *2-amino*-derivative (IV; R = NH_2) which, with nitrous and hydrobromic acids in the presence of bromine (cf. Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 231), furnished *2-bromo-4-n-propylpyridine* (IV; R = Br). The cyano-analogue (IV; R = CN) was obtained in an impure condition by distillation with cuprous cyanide (cf. Craig, *loc. cit.*; Tyson, *ibid.*, 1939, **61**, 184; McElvain and Goese, *ibid.*, 1941, **63**, 2283; Gilman and Spatz, *ibid.*, p. 1556). *2-Chloro-4-n-propylpyridine* (IV; R = Cl) could not be made to react with cuprous cyanide. Finally, the crude cyano-compound was hydrolysed to the acid by boiling with hydrochloric acid. On catalytic hydrogenation in glacial acetic acid at atmospheric pressure at *ca.* 50°, using Adams's platinic oxide catalyst, 4-propylpicolinic acid slowly absorbed three molecules of hydrogen and furnished 4-*n*-propylpipecolinic acid (I).

Experimental.

2-Benzyl-4-propylpyridine (IV; R = CH_2Ph).—4-*n*-Propylpyridine (11·0 g.), benzyl chloride (9·9 g.), and copper-bronze powder (0·1 g.) were heated in a sealed tube at 250° for 7 hours. After cooling, there was no sign of pressure on opening the tube. The contents, a dark, viscous oil containing some crystals, were not fully soluble either in ether or in water, or in dilute or concentrated hydrochloric acid, but dissolved satisfactorily in a 2-phase mixture of ether and moderately concentrated hydrochloric acid. The two layers were separated, and the aqueous layer repeatedly extracted with more ether. In this way there was removed in the ether 0·5 g. of dark extraneous matter. The aqueous acid layer was made alkaline with sodium hydroxide, and then yielded on extraction with ether 14·05 g. of an almost black, mobile oil, which, on distillation at 18 mm., furnished a middle fraction (6·56 g.), boiling mainly at 175—190°. On re-distillation the *2-benzyl-4-propylpyridine* boiled mainly at 203°/35 mm. (Found: N, 6·9. $C_{15}H_{17}N$ requires N, 6·6%). The *picrolonate* separated from acetone in yellow crystals, m. p. 171—176° (Found: N, 14·9. $C_{15}H_{17}N,C_{10}H_8O_5N_4$ requires N, 14·7%).

2-Benzoylisonicotinic Acid (V).—2-Benzyl-4-propylpyridine (1 g.) in a little dilute sulphuric acid was treated at the boil with portions of a solution of potassium permanganate (5 g.) in water (*ca.* 75 c.c.). This occupied 3·5 hours, and more sulphuric acid was added from time to time to maintain a strongly acid reaction. The total sulphuric acid used was 12·5 g. At first the permanganate was rapidly reduced, and the solution remained colourless. Later portions were attacked more slowly and gave a permanent brown precipitate of manganese dioxide which, at the end of the reaction, was filtered off hot and washed with hot water. It weighed 2·5 g., so that 10·6 atoms of oxygen were consumed. The colourless, strongly acid filtrate was extracted with ether to yield 0·64 g. of crystalline solid which was recrystallised twice from alcohol and finally from ethyl acetate. M. p. 225—230°. *2-Benzoylisonicotinic acid* is also

soluble in acetone and dioxan, but almost insoluble in hot water, benzene, or chloroform. It dissolves sparingly in aqueous sodium carbonate or dilute hydrochloric acid, but readily in concentrated acid and in aqueous caustic alkali. It gives no colour reaction with ferric chloride (Found: C, 68·8; H, 4·2; N, 6·2. $C_{14}H_9O_2N$ requires C, 68·7; H, 4·0; N, 6·2%).

2-*Amino*-4-n-*propylpyridine* (IV; R = NH_2).—(Cf. "Organic Reactions," John Wiley & Sons, 1942, Vol. 1, p. 91.) (All apparatus was dried and appropriately protected against ingress of water.) Good quality sodamide powder (36·3 g.), xylene (distilled over sodium) (80 c.c.), and three ½-inch stainless steel ball-bearings were placed in a round-bottomed 3-necked, 500 c.c. "Quickfit" flask, which was then corked and gyrated slowly and uniformly for 6 hours about a central axis inclined to the vertical. At the end of this operation the sodamide suspension was like an emulsion. 4-*n*-Propylpyridine (97·3 g.) and a further 60 c.c. of xylene were then rapidly introduced and the flask fitted with a mercury-seal stirrer, a reflux condenser, and a thermometer reaching nearly to the bottom. The mixture turned red in the cold. The flask was heated in a metal-bath at *ca.* 140°, with stirring, the xylene being kept just below the boil (internal temperature 130—135°). The reaction is exothermic, and the internal temperature rose for a short time to a point a little higher than that of the bath. Ammonia and hydrogen were evolved, and the mixture became dark brown, thickened, and deposited some tarry matter. After 12 hours the cooled contents, a stiff black paste, were thinned out with ether and poured on ice. The resulting liquid was acidified with hydrochloric acid and the ethereal layer re-extracted with acid. The combined acid extracts were made alkaline with sodium hydroxide and the precipitated base transferred to ether. This material (116 g.) on distillation at 30 mm. gave a middle fraction (83·5 g.), b. p. 125—220°, but mainly *ca.* 150°, which crystallised in the receiver. The purity of this material was adequate for use as an intermediate (yield, 76·4%). Further quantities of this product, as well as unchanged propylpyridine, were recoverable from the first (low-boiling) fraction. On re-distillation, pure 2-*amino*-4-n-*propylpyridine* was obtained. It is highly deliquescent and difficult to handle and analyse. M. p. 37—47°; b. p. 151—156°/29 mm., 145—150°/20 mm. (Found: C, 69·7; H, 8·6; N, 21·05. $C_8H_{12}N_2$ requires C, 70·6; H, 8·9; N, 20·6%). The *picrate*, from acetone, has m. p. 199—201° (Found: C, 46·1; H, 4·4. $C_8H_{12}N_2,C_6H_3O_7N_3$ requires C, 46·0; H, 4·1%). The *acetyl* derivative separates from petroleum (b. p. 60—80°) in glistening needles, m. p. 74—75°, b. p. *ca.* 200°/37 mm. (Found: C, 67·45; H, 8·1. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·9%).

2-*Chloro*-4-n-*propylpyridine* (IV; R = Cl).—To a solution of 2-amino-4-propylpyridine (4·5 g.) in concentrated hydrochloric acid (6·5 c.c.) cooled to − 17°, was added in portions powdered sodium nitrite (3·5 g.). Gas was evolved, some crystals deposited, and the liquid turned orange-yellow. The product was isolated by means of ether after adding ice and making alkaline with 25% sodium hydroxide. Yield, 3·9 g.; b. p. 130—132°/30 mm. (Found: C, 61·7; H, 6·5; Cl, 22·7. $C_8H_{10}NCl$ requires C, 61·7; H, 6·5; Cl, 22·8%).

2-*Bromo*-4-n-*propylpyridine* (IV; R = Br).—To a solution of 2-amino-4-propylpyridine (41·4 g.) in 60% hydrobromic acid (115 c.c.), cooled to − 17° and mechanically stirred, bromine (46 c.c., 143·5 g.), previously cooled to 0°, was added dropwise. A dark red precipitate was produced which was kept dispersed by stirring. During the later stages of the bromine addition the precipitate dissolved again. An ice-cold solution of sodium nitrite (52·5 g.) in water (80 c.c.) was then added at such a rate that the internal temperature could be kept at *ca.* 0°. Stirring was continued for a further hour. The mixture was then made alkaline with ice-cold 25% aqueous sodium hydroxide, the temperature being prevented from rising above *ca.* 20°. Extraction with ether furnished 58·3 g. of an oil which on distillation furnished 53·7 g. (88·3% of the theory) of 2-*bromo*-4-n-*propylpyridine*. For analysis, the oil was distilled again, the main bulk having b. p. 133—135°/19 mm. (Found: Br, 39·9. $C_8H_{10}NBr$ requires Br, 39·9%).

2-*Cyano*-4-n-*propylpyridine* (IV; R = CN) *and* 4-n-*Propylpicolinic Acid* (II).—The conversion of 2-bromo-4-*n*-propylpyridine into the corresponding cyano-compound requires the most careful control if a reasonable yield is to be obtained. The product always contains unchanged bromo-compound which cannot be wholly removed by fractionation. The crude product (containing about 20% of bromo-compound) was hydrolysed to 4-propylpicolinic acid and the 2-bromo-4-propylpyridine recovered. The reaction was carried out as follows: 2-Bromo-4-propylpyridine and ½ of its weight of dried cuprous cyanide, in a distillation flask connected to a condenser and receiver, were agitated and very gently heated with a small flame until a black homogeneous oil formed. When the temperature of the oil reached about 120° a vigorous reaction suddenly set in. At this moment the system was evacuated as rapidly as possible to about 20 mm. and the products of reaction distilled briskly. The crude distillate was redistilled once and then hydrolysed by boiling under reflux for 7 hours with 2 vols. of hydrochloric acid (17%). The product was basified, extracted with ether (to recover 2-bromo-4-propylpyridine which was reprocessed), reacidified, neutralised with ammonia, and treated with copper sulphate solution in slight excess. Crude *copper 4-propylpicolinate* separated as a bluish-grey precipitate (yield 80 g. from 160 g. of bromo-compound; 40·9% of theory); it forms large brilliant blue needles from alcohol, m. p. 305° (decomp.) and is almost insoluble in water, acetone, or chloroform [Found: C, 55·2; H, 5·2; Cu, 15·45. $(C_9H_{10}O_2N)_2Cu$ requires C, 55·2; H, 5·1; Cu, 16·2%]. The free *acid* was obtained by passing hydrogen sulphide for many hours through a boiling suspension of the finely powdered copper salt (42 g.) in 50% alcohol (1200 c.c.); the copper sulphide thus formed was colloidal and, after evaporation of the alcohol, was removed by a twice repeated treatment of the boiling solution with charcoal (2 g.), followed by filtration through kieselguhr. The filtrate on evaporation left a crystalline residue (36·3 g.) which after several crystallisations from acetone formed colourless pyramids, m. p. 104—107° (Found: C, 65·6; H, 6·7; N, 8·45. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5%).

4-n-*Propylpipecolinic Acid* (I).—The foregoing acid in acetic acid solution at *ca.* 50°, and in the presence of highly active Adams's platinic oxide catalyst, absorbs hydrogen at atmospheric pressure slowly, and the absorption is liable to tail off unless periodically reactivated either by the addition of more catalyst or by flushing the system with oxygen. 4-Propylpicolinic acid (29 g.) in glacial acetic acid (250 c.c.) was reduced under the conditions stated in the presence of 1·4 g. of catalyst. Total absorption, 11·8 l. at N.T.P.; calc. for substance and 1·4 g. catalyst, 12·0 l. The catalyst was filtered off, the acetic acid removed under reduced pressure, and the crystalline residue triturated with ethyl acetate. On filtering, a solid was obtained, which still smelled of acetic acid, even after much washing with ethyl acetate in which it is almost insoluble. The acetic acid was driven off by drying for several hours at 110°; the 4-n-*propylpipecolinic acid* so obtained (yield amost quantitative) separated from alcohol in gleaming white felted needles, m. p. 284° (decomp.) after softening. It is soluble in water, alcohol, benzene, and chloroform, but very sparingly in ether, ethyl acetate, or acetone (Found: C, 62·9; H, 9·9; N, 8·25. $C_9H_{17}O_2N$ requires C, 63·1; H, 10·0; N, 8·2%). The N-*benzoyl* derivative prepared by the method of Steiger (*J. Org. Chem.*, 1944, **9**, 396) is an oil which, on esterification with methyl alcohol and hydrogen chloride, furnished *methyl* N-*benzoyl*-4-n-*propylpipecolinate*, a straw-coloured, viscous oil, b. p. 190°/0·2 mm., 232—234°/16 mm., and 244—246°/25·5 mm. (Found: C, 70·7; H, 8·35. $C_{17}H_{23}O_3N$ requires C, 70·55; H, 8·0%).

The author is much indebted to Messrs. A. W. Stokes and H. Waddington, and his thanks are due to A. Bennett for the microanalyses.

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204. *Researches on Acetylenic Compounds. Part VI. Carbinols derived from Methyl β-Chlorovinyl Ketone and their Conversion into Unsaturated Aldehydes.*

By E. R. H. Jones and B. C. L. Weedon.

Methyl β-chlorovinyl ketone reacts with sodium acetylide in liquid ammonia giving a 45% yield of the carbinol (II) and with the Grignard complexes from 1-hexyne and vinylacetylene to give similar carbinols (IV; R = *n*-Bu and CH:CH_2 respectively) in about 90% yields. On treatment with dilute acids all three carbinols undergo anionotropic rearrangement followed by elimination of hydrogen chloride, yielding conjugated acetylenic–ethylenic aldehydes of type (III). Rearrangement-halogenation occurs with concentrated hydrochloric acid and leads to 1 : 1-dichloro-compounds such as (VI). Light-absorption data for the latter and for the aldehydes, their semicarbazones, and their 2 : 4-dinitrophenylhydrazones are recorded.

The carbinol obtained by reaction of the chlorovinyl ketone with methylmagnesium bromide is similarly converted into β-methylcrotonaldehyde in about 30% yield. This may well develop into a useful general method of synthesising otherwise difficultly accessible αβ-ethylenic aldehydes.

The isomerisation of acetylenic carbinols and glycols, derived from αβ-ethylenic aldehydes and ketones, in the presence of acids, to conjugated ethylenic–acetylenic carbinols and glycols, *e.g.*,

$$HC{\equiv}C{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}CH_3 \longrightarrow HC{\equiv}C{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH_3$$

has been extensively investigated in these laboratories (see *J.*, 1943, 261—270; 1944, 134—147, 436; 1945, 77—94). It seemed probable that the carbinols obtained by condensation of acetylenic compounds with β-chlorovinyl ketones would, on treatment with acids, be converted into conjugated acetylenic–ethylenic aldehydes, following elimination of hydrogen chloride from the unstable intermediates.

$$\underset{\text{(I.)}}{Me{\cdot}CO{\cdot}CH{=}CHCl} \xrightarrow{C_2H_2} \underset{\text{(II.)}}{HC{\equiv}C{\cdot}CMe(OH){\cdot}CH{=}CHCl} \xrightarrow{\text{acids}} [HC{\equiv}C{\cdot}CMe{=}CH{\cdot}CH(OH)Cl] \longrightarrow \underset{\text{(III.)}}{HC{\equiv}C{\cdot}CMe{=}CH{\cdot}CHO}$$

Methyl β-chlorovinyl ketone (I) was chosen for this study because of its ready availability by condensation of acetyl and vinyl chlorides in the presence of aluminium chloride. It suffers from the disadvantage, however, of being rather unstable, and has to be used immediately after preparation. By interaction with an equimolecular quantity of 1-hexynylmagnesium bromide in ethereal solution *1-chloro-3-methylnon-1-en-4-yn-3-ol* (IV; R = *n*-Bu) was obtained in 45% yield, but, when the proportion of Grignard reagent was doubled

$$\text{(IV.)}\quad RC{\equiv}C{\cdot}CMe(OH){\cdot}CH{=}CHCl \xrightarrow{\text{dil. } H_2SO_4} RC{\equiv}C{\cdot}CMe{=}CH{\cdot}CHO \quad \text{(V.)}$$

$$RC{\equiv}C{\cdot}CMe(OH){\cdot}CH{=}CHCl \xrightarrow{\text{conc. HCl}} RC{\equiv}C{\cdot}CMe{=}CH{\cdot}CHCl_2 \quad \text{(VI.)}$$

and the reaction carried out in boiling ethereal solution, the yield of the desired carbinol was increased to 95%. Employing an identical procedure vinylacetylene gave an 85% yield of the corresponding *carbinol* (IV; R = CH=CH_2).

From previous experience of condensations of αβ-unsaturated ketones with sodium acetylide in liquid ammonia (Cymerman, Heilbron, and Jones, *J.*, 1945, 90) it was to be expected that the yield of carbinol from methyl β-chlorovinyl ketone would be very dependent upon the proportions of reactants employed. In the case of methyl vinyl ketone the yield was found to increase with increasing proportions of acetylide, reaching 40% when 4·5 moles of sodium acetylide were used. Equimolecular proportions of the acetylide and the chlorovinyl ketone gave a 20% yield of the *carbinol* (II); an acetylide : ketone ratio of 2 : 1 gave a 45% yield, but this was reduced to about 10% when the proportion was further increased to 3 : 1. The optimum conditions, which have yet to be determined, are obviously quite critical.

All three carbinols described above were converted into aldehydes in good yields on treatment with dilute acids, but rather different conditions were necessary in the three cases on account of the different solubilities of the carbinols. With the simplest carbinol (II), a 70% yield of the *aldehyde* (III) was obtained simply by treatment with dilute sulphuric acid at 20°. The vinyl acetylenic carbinol (IV; R = CH=CH_2) gave the *aldehyde* (V; R = CH=CH_2) in 60% yield in dilute sulphuric acid–dioxan, but the *aldehyde* (V; R = *n*-Bu) could only be obtained in reasonable yield by using trimethylcetylammonium bromide to emulsify the carbinol in a dilute sulphuric acid–dioxan medium.

The light-absorption data for alcoholic solutions of these aldehydes and of their *semicarbazones* and *2 : 4-dinitrophenylhydrazones* are detailed in Table I. In general they are in agreement with expectations, except that in the case of the dinitrophenylhydrazone of the aldehyde (V; R = CH=CH_2), no bathochromic effect corresponding to the presence of the additional conjugated ethenoid linkage is apparent, although such an effect is observed with both the aldehyde itself and its semicarbazone.

When acetylenylcarbinols derived from αβ-unsaturated carbonyl compounds are treated with concentrated hydrochloric acid, rearrangement-halogenation is readily effected (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77):

$$CH_3{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH \longrightarrow CH_3{\cdot}CHCl{\cdot}CH{=}CH{\cdot}C{\equiv}CH$$

TABLE I.

	2 : 4-Dinitrophenylhydrazone.				Semicarbazone.	
	$\lambda_{max.}$, A.	$\epsilon_{max.}$	$\lambda_{max.}$, A.	$\epsilon_{max.}$	$\lambda_{max.}$, A.	$\epsilon_{max.}$
HC≡C·CMe=CH·CHO	2615	12,500	2600	15,500	2920	32,500
			3850	33,500		
n-BuC≡C·CMe=CH·CHO	2700	14,000	2640 †	17,500	2950	35,000
	2760	14,000	3050	10,000	3060 *	31,000
			3900	32,000		
CH_2=CH·C≡C·CMe=CH·CHO	2200	9,000	2670 †	18,000	3080	27,500
	2820	12,000	3080	10,000		
	2920	12,000	3900	40,000		
	3000	11,500				
HC≡C·CH=CH·CO·Me [1]	2550	11,500	3780 †	30,000		

[1] Bowden, Heilbron, Jones, and Weedon, this vol., p. 39. * Inflexion. † In chloroform.

The above-mentioned carbinols prepared from methyl β-chlorovinyl ketone behave similarly, the dichloro-compounds (VI) (listed in Table II, where their light-absorption properties are recorded) being produced in yields ranging from 55—85%.

TABLE II.

	$\lambda_{max.}$, A.	$\epsilon_{max.}$		$\lambda_{max.}$, A.	$\epsilon_{max.}$
HC≡C·CMe=CH·$CHCl_2$	2290	13,000	HC≡C·CH=CH·CH_2Cl [1]	2280	10,500
n-BuC≡C·CMe=CH·$CHCl_2$	2370	15,000	CH_2=CH·C≡C·CH=CH·CHCl·CH_3 [1]	2200	6,000
CH_2=CH·C≡C·CMe=CH·$CHCl_2$	2610	14,500		2620	17,000
	2760 *	11,500		2750 *	13,500

[1] Heilbron, Jones, Lacey, McCombie, and Raphael, *loc. cit.* * Inflexion.

With anionotropic systems of the type

(VII.) RCH(OH)·CH=CH_2 ⇌ RCH=CH·CH_2·OH (VIII.)

the conversion of (VII) into (VIII) in the presence of acids is usually quantitative when R = aryl, acetylenyl, or vinyl (see *inter alia*, Burton and Ingold, *J.*, 1928, 904; Burton, *J.*, 1928, 1650; Jones and McCombie, *J.*, 1943, 261; Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84), but when R = alkyl, the mobility of the system is markedly diminished (Baudrenghien, *Bull. Soc. chim. Belg.*, 1922, **31**, 160; Burton, *J.*, 1929, 455; 1930, 248) and in the simplest cases the systems only become actively tautomeric when the hydroxyl group is replaced by a halogen atom, etc. (Young and Lane, *J. Amer. Chem. Soc.*, 1937, **59**, 2051; 1938, **60**, 847; Baudrenghien, *loc. cit.*). The mobility of such systems is considerably enhanced, however, if a *gem*-dialkyl group is present, as in dimethylvinylcarbinol (Locquin and Wouseng, *Compt. rend.*, 1922, **174**, 1711; **175**, 100; Sung, *Ann. Chim.*, 1924, **1**, 386) and it seemed possible, as an extension of the work already described in this paper, that in the presence of acids, simple chlorovinylcarbinols (*e.g.*, IX) might be converted into αβ-ethylenic aldehydes, *e.g.* (XI),

$$Me_2C(OH)\cdot CH{=}CHCl \rightleftharpoons Me_2C{=}CH\cdot CH(OH)Cl \longrightarrow Me_2C{=}CH\cdot CHO$$
(IX.) (X.) (XI.)

the equilibrium (IX ⇌ X) being disturbed by the elimination of hydrogen chloride from the isomeric chloro-carbinols (*e.g.*, X). Such a conversion has now been realised. The *carbinol* (IX), obtained by reaction of methyl β-chlorovinyl ketone with methylmagnesium bromide, yields β-methylcrotonaldehyde (XI) on treatment with 10% sulphuric acid at room temperature. We intend to study this reaction in more detail as opportunity permits, since, although only a 30% yield of aldehyde was obtained in the single experiment so far carried out, the method promises to be of such wide applicability that a detailed study of reaction conditions appears desirable.

EXPERIMENTAL.

(Absorption spectra were determined in alcoholic solutions.)

1-Chloro-3-methylpent-1-en-4-yn-3-ol (II).—A solution of sodium acetylide (from sodium, 28 g.) in liquid ammonia (750 c.c.) was prepared *via* sodamide using sodium oxide (from sodium 0·8 g.) and hydrated ferric nitrate (0·24 g.) in the manner previously described (Heilbron, Jones, and Weedon, *J.*, 1945, 81). Freshly prepared methyl β-chlorovinyl ketone (62·5 g.; B.P. 466,891; U.S.P. 2,137,664) in ether (100 c.c.) was added during 1 hour, the mixture was stirred for a further 2½ hours, and then the reaction was terminated by the gradual addition of ammonium chloride (66 g.). The ammonia was allowed to evaporate overnight and the product isolated by filtration and careful washing of the residue with ether. The combined ethereal solutions were dried and evaporated and gave *1-chloro-3-methylpent-1-en-4-yn-3-ol* (35 g.), b. p. 91°/50 mm., 75°/20 mm., 64°/12 mm., $n_D^{18°}$ 1·4785 (Found: C, 54·95; H, 5·45. C_6H_7OCl requires C, 55·2; H, 5·4%).

1-Chloro-3-methylnon-1-en-4-yn-3-ol (IV; R = *n*-Bu).—1-Hexyne (55 g.) in ether (50 c.c.) was added over 1 hour to a stirred solution (700 c.c.) of ethylmagnesium bromide (from magnesium, 16·2 g.) and the mixture was refluxed for 3 hours. Freshly prepared methyl β-chlorovinyl ketone (42 g.) in ether (60 c.c.) was added with cooling (ice) during

2 hours and the stirring continued for 30 minutes at room temperature and finally for 1 hour under reflux. Decomposition with ammonium chloride (ice) followed by isolation by means of ether gave 1-*chloro*-3-*methylnon*-1-*en*-4-*yn*-3-*ol* (69·9 g.), b. p. 77—78·5°/0·3 mm., 59°/0·1 mm., $n_D^{17°}$ 1·4818 (Found: C, 64·55; H, 8·15. $C_{10}H_{15}OCl$ requires C, 64·35; H, 8·1%).

1-*Chloro*-3-*methylhepta*-1 : 6-*dien*-4-*yn*-3-*ol* (IV; R = $CH{:}CH_2$).—A solution of vinylacetylene [52 g. (crude) made according to Schmitz and Schumacher, *Z. Electrochem.*, 1939, **45**, 503] in ether (150 c.c.) was added during 1 hour to a stirred ethereal solution (500 c.c.) of ethylmagnesium bromide (from magnesium 24 g.) contained in a three-necked flask fitted with a double surface condenser containing solid carbon dioxide. The mixture was refluxed for 2 hours, ecooled, and then treated dropwise with a solution of freshly prepared methyl β-chlorovinyl ketone (52 g.) in ether (100 c.c.) during 1 hour. Stirring was continued for 30 minutes at room temperature and finally, after dilution of the solution to 1 l. with ether, under reflux for 1 hour. Decomposition with ammonium chloride (110 g.) and ice followed by isolation by means of ether gave 1-*chloro*-3-*methylhepta*-1 : 6-*dien*-4-*yn*-3-*ol* (67 g.), b. p. 78°/1 mm., 60°/0·4 mm., 46°/0·1 mm., 37°/0·05 mm., $n_D^{17°}$ 1·5168 (Found: C, 60·6, 60·0; H, 6·0, 5·8. C_9H_9OCl requires C, 61·35; H, 5·8%). Light absorption: Maxima, 2230, 2320 A.; ϵ = 14,500 and 12,500 respectively.

3-*Methylpent*-2-*en*-4-*yn*-1-*al* (III).—A solution of 1-chloro-3-methylpent-1-en-4-yn-3-ol (5 g.) in dilute sulphuric acid (400 c.c.; 10% w/v) containing a trace of quinol was kept at room temperature for 42 hours. It was then saturated with ammonium sulphate and extracted thoroughly with ether. Evaporation of the ethereal solution and distillation of the residue gave 3-*methylpent*-2-*en*-4-*yn*-1-*al* (2·6 g.) as a pale yellow, lachrymatory liquid that undergoes partial polymerisation even in the presence of quinol, both on distillation and on keeping. B. p. 71—73°/50 mm., 53—54°/20 mm., $n_D^{23°}$ 1·4993 (Found: C, 76·7, 76·35; H, 6·65, 6·6. C_6H_6O requires C, 76·6; H, 6·4%). The 2 : 4-*dinitrophenylhydrazone* formed small red needles from alcohol, m. p. 144—145° (Found: N, 20·7. $C_{12}H_{10}O_4N_4$ requires N, 20·45%). The *semicarbazone* crystallised in needles from aqueous alcohol, m. p. 180° (decomp.; bath preheated to 160°) (Found: N, 27·5. $C_7H_9ON_3$ requires N, 27·8%).

3-*Methylnon*-2-*en*-4-*yn*-1-*al* (V; R = *n*-Bu).—A mixture of 1-chloro-3-methylnon-1-en-4-yn-3-ol (20 g.), dilute sulphuric acid (1800 c.c.; 10% w/v), dioxan (900 c.c.), and trimethylcetylammonium bromide (1 g.) was stirred vigorously for 48 hours at 45—50° in nitrogen, and the product was then isolated by means of ether. Distillation gave 3-*methylnon*-2-*en*-4-*yn*-1-*al* (*ca.* 10 g.) as a very pale yellow liquid, b. p. 78—82°/1 mm., $n_D^{16°}$ 1·4982 (Found: C, 79·75; H, 9·55. $C_{10}H_{14}O$ requires C, 79·95; H, 9·4%). The 2 : 4-*dinitrophenylhydrazone* formed red needles from methyl alcohol, m. p. 109·5—110° (Found: N, 17·3. $C_{16}H_{18}O_4N_4$ requires N, 16·95%). The *semicarbazone* crystallised in leaflets from aqueous alcohol, m. p. 143—144° (Found: N, 20·3. $C_{11}H_{17}ON_3$ requires N, 20·25%).

3-*Methylhepta*-2 : 6-*dien*-4-*yn*-1-*al* (V; R = $CH{:}CH_2$).—A solution of 1-chloro-3-methylhepta-1 : 6-dien-4-yn-3-ol (10·5 g.) in dioxan (450 c.c.) and dilute sulphuric acid (1 l.; 10% w/v) was kept at room temperature for 24 hours. Dilution with water to 2·5 l. and isolation by means of ether gave 3-*methylhepta*-2 : 6-*dien*-4-*yn*-1-*al* (4·2 g.) as a pale yellow mobile liquid, b. p. 51°/1 mm.; 46—48°/0·4 mm., $n_D^{19°}$ 1·5582 (Found: C, 79·6; H, 6·95. C_8H_8O requires C, 80·0; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised as dark red needles from methyl alcohol, m. p. 148—149° (Found: N, 18·6. $C_{14}H_{12}O_4N_4$ requires N, 18·65%). The *semicarbazone* formed pale yellow needles from aqueous alcohol, m. p. 180—181° (Found: N, 23·9. $C_9H_{11}ON_3$ requires N, 23·7%).

1 : 1-*Dichloro*-3-*methylpent*-2-*en*-4-*yne* (VI; R = H).—1-Chloro-3-methylpent-1-en-4-yn-3-ol (5 g.) and concentrated hydrochloric acid (100 c.c.) were shaken together at room temperature in nitrogen for 45 minutes. After dilution with water to 200 c.c. the product was isolated by means of ether. Distillation gave 1 : 1-*dichloro*-3-*methylpent*-2-*en*-4-*yne* (3·8 g.), b. p. 72—73°/50 mm., 49—50°/18 mm., $n_D^{16°}$ 1·4989 (Found: C, 48·7; H, 4·35. $C_6H_6Cl_2$ requires C, 48·35; H, 4·05%).

1 : 1-*Dichloro*-3-*methylnon*-2-*en*-4-*yne* (VI; R = *n*-Bu).—A mixture of 1-chloro-3-methylnon-1-en-4-yn-3-ol (15 g.) and concentrated hydrochloric acid (1 l.) was shaken at 20° in nitrogen for 2½ hours. Dilution with water to 2·5 l. and isolation of the product with ether gave 1 : 1-*dichloro*-3-*methylnon*-2-*en*-4-*yne* (14·3 g.) as a pale yellow oil, b. p. 84—86°/0·6 mm., 57—59°/0·15 mm., 50—51°/0·05 mm., $n_D^{20°}$ 1·4990 (Found: C, 58·6; H, 7·0. $C_{10}H_{14}Cl_2$ requires C, 58·55; H, 6·9%).

1 : 1-*Dichloro*-3-*methylhepta*-2 : 6-*dien*-4-*yne* (VI; R = $CH{:}CH_2$).—1-Chloro-3-methylhepta-1 : 6-dien-4-yn-3-ol (10 g.) and concentrated hydrochloric acid (450 c.c.) were shaken at 20° in nitrogen for 3 hours. Dilution to 1200 c.c. with water and isolation of the product with ether gave 1 : 1-*dichloro*-3-*methylhepta*-2 : 6-*dien*-4-*yne* (6·3 g.) as a pale yellow oil, b. p. 75—76°/2·5 mm., 24°/0·05 mm., $n_D^{16°}$ 1·5444 (Found: Cl, 39·4. $C_8H_8Cl_2$ requires Cl, 40·5%).

1-*Chloro*-3-*methylbut*-1-*en*-3-*ol* (IX).—Freshly prepared methyl β-chlorovinyl ketone (20 g.) in ether (40 c.c.) was added during 1 hour to methylmagnesium bromide (from magnesium 7 g.) in ether (500 c.c.) and, after 30 minutes' stirring at room temperature, the organometallic complex, which had separated out as a sticky, orange coloured solid, was decomposed with a solution of ammonium chloride (50 g.) in water. Isolation by means of ether and fractional distillation through a Dufton column (24 cm.) gave 1-*chloro*-3-*methylbut*-1-*en*-3-*ol* (11 g.), b. p. 55°/15 mm., $n_D^{18°}$ 1·4590 (Found: C, 50·3, 49·75; H, 7·5, 7·95. C_5H_9OCl requires C, 49·8; H, 7·5%). A better yield would doubtless have been obtained by carrying out the Grignard condensation in benzene solution.

β-*Methylcrotonaldehyde* (XI).—A solution of the above 1-chloro-3-methylbut-1-en-3-ol (3 g.) in dilute sulphuric acid (250 c.c.; 10% w/v) was kept at room temperature in nitrogen for 3 days, during which time an oil separated. The crude product was isolated by means of ether and divided into two equal portions. The first was treated with semicarbazide acetate in aqueous alcoholic solution and gave the semicarbazone of β-methylcrotonaldehyde (0·45 g.; 25%) as needles from methyl alcohol, m. p. 219·5—220·5°, undepressed on admixture with an authentic specimen (m. p. 221—222°). Light absorption: Maxima, 2700 and 2780 A.; ϵ = 33,000 (Evans and Gillam, *J.*, 1943, 565, give maximum, 2730 A.; ϵ = 33,500). The second portion was treated with a methyl-alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate and gave the 2 : 4-dinitrophenylhydrazone of β-methylcrotonaldehyde (1·1 g.; 32%) as dark red needles from alcohol, m. p. 182—183° undepressed on admixture with an authentic specimen (m. p. 179°). Light absorption: Main maximum, 3800 A.; ϵ = 28,500 (Braude and Jones, *J.*, 1945, 498, give 3820 A.; ϵ = 24,000).

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205. *Researches on Acetylenic Compounds. Part VII. Reactions of 2-Chlorohex-3-en-5-yne and Related Compounds with Ammonia and Amines. Reversed Anionotropic Rearrangements accompanying Replacement.*

By E. R. H. Jones, R. N. Lacey, and Peter Smith.

In systems of the type (A), such as is present in 2-chlorohex-3-en-5-yne, replacement reactions with amines either proceed normally (giving B) or else are accompanied by anionotropic rearrangements when amines of type

$$\underset{\text{(B)}}{\text{—CHX·CH=CH·C≡C—}} \longleftarrow \underset{\text{(A)}}{\text{—CHCl·CH=CH·C≡C—}} \longrightarrow \underset{\text{(C)}}{\text{—CH=CH·CHX·C≡C—}}$$

(C) result. The structures of these abnormal products have been ascertained from light-absorption data and ozonolysis experiments. It has been shown that increasing base strength of the substituting amine (XH) tends to promote the formation of isomerised products, which tendency is also favoured by the presence of substituents known to enhance the mobility of the hydroxyl group in the parent oxotropic systems, *e.g.*:

$$\text{—CH=CH·CH(OH)·C≡C—} \longrightarrow \text{—CH(OH)·CH=CH·C≡C—}$$

In a previous publication (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77) the simultaneous rearrangement and replacement chlorination which occurs when acetylenic carbinols and glycols derived from αβ-ethylenic aldehydes are treated with concentrated hydrochloric acid at room temperature has been described. Thus propenylethynylcarbinol readily yields 2-chlorohex-3-en-5-yne (I) under these conditions, whereas on shaking with dilute sulphuric or other acids, the corresponding alcohol, hex-3-en-5-yn-2-ol (II) (Jones and McCombie, *J.*, 1943, 261) is produced.

$$\text{CH}_3\text{·CH=CH·CH(OH)·C≡CH} \xrightarrow{\text{conc. HCl}} \text{CH}_3\text{·CHCl·CH=CH·C≡CH} \quad \text{(I.)}$$

$$\text{CH}_3\text{·CH=CH·CH(OH)·C≡CH} \xrightarrow{\text{dil. H}_2\text{SO}_4} \text{CH}_3\text{·CH(OH)·CH=CH·C≡CH} \quad \text{(II.)}$$

The behaviour of compounds of the type (I) on treatment with ammonia and amines has now been studied. Replacement reactions occur readily in every case and, as would be expected, the best yields are obtained with secondary amines, whereas ammonia and primary amines give rise to considerable quantities of undistillable secondary and/or tertiary amines. Simple replacement, however, is not the only reaction which has been encountered, and the products obtained can be differentiated sharply into two groups, depending both upon the nature of the chloro-compound and upon the particular base employed.

Normal Reactions.—When 2-chlorohex-3-en-5-yne (I) is treated with ammonia, ethylamine, or aniline, the expected *amines* (III, IV, or V respectively) are obtained.

$$\text{(I.) HC≡C·CH=CH·CHCl·CH}_3 \xrightarrow{\text{NH}_3} \text{HC≡C·CH=CH·CH(NH}_2\text{)·CH}_3 \quad \text{(III.)}$$

$$\text{(I.) HC≡C·CH=CH·CHCl·CH}_3 \xrightarrow{\text{EtNH}_2} \text{HC≡C·CH=CH·CH(NHEt)·CH}_3 \quad \text{(IV.)}$$

$$\text{(I.) HC≡C·CH=CH·CHCl·CH}_3 \xrightarrow{\text{PhNH}_2} \text{HC≡C·CH=CH·CH(NHPh)·CH}_3 \quad \text{(V.)}$$

The light-absorption properties of these bases and their *hydrochlorides* are typical of those of conjugated vinylacetylene systems (Table I) (cf. Jones and McCombie, *loc. cit.*, and later papers in the same series) and the assigned structures received further confirmation from Zerewitinoff determinations.

The reaction between the same chloro-compound (I) and the stronger base, diethylamine, is anomalous, however, and is discussed in detail below. On the other hand, even with this base, the chloro-compounds (VII; R = H or *n*-Bu), derived from acraldehyde carbinols (VI) by hydrochloric acid treatment, behave in

$$\text{(VI.)} \quad \text{RC≡C·CH(OH)·CH=CH}_2 \xrightarrow{\text{conc. HCl}} \text{(VII.)} \quad \text{RC≡C·CH=CH·CH}_2\text{Cl} \xrightarrow{\text{Et}_2\text{NH}} \text{RC≡C·CH=CH·CHNEt}_2 \quad \text{(VIII.)}$$

the normal manner, giving *amines* (VIII; R = H or *n*-Bu) which, as well as their *hydrochlorides*, exhibit typical vinylacetylene absorption (Table I).

The dichloro-compound (IX) obtained from crotonaldehyde acetylene glycol reacts with both methyl- and

$$\text{(IX.)} \quad \text{CH}_3\text{·CHCl·CH=CH·C≡C·CH=CH·CHCl·CH}_3 \xrightarrow{\text{MeNH}_2} \text{CH}_3\text{·CH(NHMe)·CH=CH·C≡C·CH=CH·CH(NHMe)·CH}_3 \quad \text{(X.)}$$

ethyl-amines giving *amines* (*e.g.*, X), which show light absorption similar to that of the parent compound (IX), characteristic of the conjugated divinylacetylene chromophore (Table I).

Abnormal Reactions.—The chloro-compound (I) reacts smoothly with diethylamine either at 100° or at 20° for a much longer time giving a tertiary *amine* in excellent yield, but the product, unlike the amines described

TABLE I.

	$\lambda_{max.}$, A.	$\epsilon_{max.}$
NHPh·CHMe·CH=CH·C≡CH	2260	17,500
	2400	17,500
Hydrochloride	2280	19,000
NHEt·CHMe·CH=CH·C≡CH	2230	13,000
Hydrochloride	2230	15,000
NH_2·CHMe·CH=CH·C≡CH	2235	11,000
	2280 *	9,500
Hydrochloride	2230	14,000
	2340 *	9,500
NEt_2·CH_2·CH=CH·C≡CH	2230	12,500
Hydrochloride	2250	15,500
	2340 *	12,000
NEt_2·CH_2·CH=CH·C≡CBu (*n*)	2280	16,000
	2370 *	15,500
CHMeCl·CH=CH·C≡CH [1]	2260	14,000
CH_3·CH(OH)·CH=CH·C≡CH [2]	2230	13,500
	2300 *	9,500
CH_2·CH(NHR)·CH=CH·C≡C·CH=CH·CH(NHR)·CH_3		
(R = Me)	2200	10,000
	2290	10,000
	2660	16,500
	2750 *	14,500
(R = Et)	2650	17,000
	2730 *	15,500
CH_3·CHCl·CH=CH·C≡C·CH=CH·CHCl·CH_3 [1]	2210	11,500
	2700	19,500
	2760	18,500

[1] Heilbron, Jones, Lacey, McCombie, and Raphael, *loc. cit.*
[2] Jones and McCombie, *loc. cit.*
* Inflexion.

above, shows no high-intensity absorption in the ultra-violet and its hydrochloride is similarly transparent. Consequently it cannot contain any conjugated system, either of the vinylacetylene type or of the type (C=C—N) which, as recently demonstrated (Bowden, Braude, Jones, and Weedon, this vol., p. 45) absorbs strongly in the 2200A. region. Further, since an ethynyl hydrogen atom is still present (silver derivative and Zerewitinoff) the only reasonable structure for this compound is (XI), its formation from the chloro-compound thus involving substitution together with a reversal of the well established anionotropic rearrangement by which

(I.) CH_3·CHCl·CH=CH·C≡CH $\xrightarrow{NHEt_2}$ CH_2·CH=CH·CH(NEt$_2$)·C≡CH (XI.)

(XII.) CH_3·CHCl·CH=CH·C≡CBu(*n*) ⟶ CH_3·CH=CH·CH(NEt$_2$)·C≡CBu(*n*) (XIII.)

the conjugated vinylacetylene system is originally formed. The *amine* (XIII), obtained from the halogeno-compound (XII) also in excellent yield, is analogously formulated in view of its light absorption properties and those of its hydrochloride.

Further confirmation of the structures (XI and XIII) assigned to these anomalous products is afforded by the results of ozonolysis experiments. Yields of acetaldehyde (estimated as its dimedon derivative) of 40 and 25% respectively are obtained, comparing favourably with a 45% yield resulting from the application of an identical procedure to propenylethynylcarbinol. Also, the behaviour of the amine (XI) on hydrogenation in the presence of a platinum catalyst appears to be typical of the location of the amino-group between the two unsaturated centres. In methanol solution four molecular equivalents of hydrogen are absorbed and an almost quantitative yield of diethylamine (as hydrochloride) results. Less fission of the carbon–nitrogen bond occurs in *cyclo*hexane solution. Mannich, Handke, and Roth (*Ber.*, 1936, **69**, 2112) observed similar fissions and variations according to the polar nature of the solvent employed while hydrogenating some diamines of the type $-\overset{\alpha}{C}H(NR_2)\cdot CH{=}CH\cdot NR_2$ (cf. also Meisenheimer and Link, *Annalen*, 1930, **479**, 211). Hydrogenolysis was confined to the amino-group attached to the α-carbon atom.

When the divinylacetylene chloro-compound (XIV) reacts with diethylamine the *product* (XV) exhibits light absorption (Table II) indicative of the presence of only a simple conjugated vinylacetylene system.

(XIV.) CH_3·CHCl·CH=CH·C≡C·CMe=CHMe ⟶ CH_3·CH=CH·CH(NEt$_2$)·C≡C·CMe=CHMe (XV.)

CH_3·CH(NMe$_2$)·CH=CH·C≡C·CH=CH·CH(NMe$_2$)·CH_3 (XVI.)

CH_3·CH=CH·CH(NR$_2$)·C≡C·CH=CH·CH(NR$_2$)·CH_3 (XVII.)

CH_3·CH=CH·CH(NEt$_2$)·C≡C·CH(NEt$_2$)·CH=CH·CH_3 (XVIII.)

According to light-absorption data (Table II) the product of the reaction of the dichloro-compound (IX) with dimethyl- or diethyl-amine is a mixture of (XVI) and (XVII; R = Me), or (XVII; R = Et) and (XVIII) respectively, the use of the stronger base resulting in the formation of none of the normal product. Ozonolysis of the mixture of (XVII; R = Et) and (XVIII) gave about 20% of the theoretical yield of acetaldehyde.

TABLE II.

	$\lambda_{max.}$, A.	$\epsilon_{max.}$
$CH_3\cdot CH{=}CH\cdot CH(NEt_2)\cdot C{\equiv}C\cdot CMe{=}CHMe$	2280	13,000
$CH_3\cdot CH{=}CH\cdot CH(NMe_2)\cdot C{\equiv}C\cdot CH{=}CH\cdot CH(NMe_2)\cdot CH_3$	2290	9,500
$CH_3\cdot CH(NMe_2)\cdot CH{=}CH\cdot C{\equiv}C\cdot CH{=}CH\cdot CH(NMe_2)\cdot CH_3$	2670	8,000

Discussion.—A sufficient number of examples of both normal and anomalous replacement reactions has been encountered in the present study to enable certain general conclusions to be drawn concerning the factors involved in determining the nature of the final product.

With ammonia, and also the weak primary amines, ethylamine and aniline, 2-chlorohex-3-en-5-yne (I) undergoes simple replacement, but with the stronger base, diethylamine, rearrangement accompanies the substitution reaction. Similarly, the dichloro-compound (XIV) behaves normally with both methylamine and ethylamine, some isomerisation occurs with dimethylamine, and this is considerably more extensive with diethylamine. Increasing base strength thus tends to promote the formation of abnormal products.

In oxotropic systems of the type:

$$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\overset{3}{C}H(OH){-}\overset{4}{C}{\equiv}\overset{5}{C}H \longrightarrow CH_2\cdot CH{=}CH\cdot C{\equiv}CH \quad (OH)$$

kinetic studies (Braude and Jones, this vol., p. 122) have revealed that replacement of the hydrogen atoms at C_1, C_3, and C_5 by alkyl groups has a profound enhancing effect upon the velocity of the acid-catalysed rearrangement. Thus under comparable conditions introduction of a methyl group at C_1 increases the velocity constant by a factor of 3000, at C_3 the factor for this group is 500 whereas a *n*-butyl group at C_5 steps up the velocity constant 300 times. In the present studies it has been observed, in a qualitative fashion, that groups which increase the mobility of the above oxotropic system are apparently similarly effective in promoting the reversed rearrangement during these amine replacement reactions. Thus the rearrangement of the carbinols (VI; R = H and *n*-Bu) to the corresponding primary alcohols with acids is only effected with difficulty (the relative *k*'s are respectively 0·0003 and 0·1 when compared with 1 for propenylethynylcarbinol) and, even with the strongest base used in the present study, amination of the corresponding chloro-compound (VII) proceeds without rearrangement. The chloro-compounds (I, XII, and XIV) derived by hydrochloric acid treatment from much more readily isomerised carbinols all undergo anomalous reactions on heating with diethylamine.

Somewhat similar reversals of anionotropic rearrangements accompanying substitution reactions have been observed by Meisenheimer and Link (*loc. cit.*). On treatment of cinnamyl chloride with both aqueous-alcoholic potassium hydroxide and potassium acetate in acetic acid, mixtures of derivatives of cinnamyl alcohol and phenylvinylcarbinol are obtained.

$$PhCH{=}CH\cdot CH_2Cl \longrightarrow PhCH{=}CH\cdot CH_2X + PhCHX\cdot CH{=}CH_2$$

With *alcoholic* potassium hydroxide, on the other hand, no isomerisation occurs, the product consisting entirely of cinnamyl ethyl ether. It may also be noted that prolongation of the treatment of cinnamyl chloride with potassium acetate in acetic acid results in the formation of a greater proportion of cinnamyl acetate, owing to the isomerisation of the phenylvinylcarbinyl acetate under these conditions. This effectively demonstrates that the abnormal product (*i.e.*, phenylvinylcarbinyl acetate) does not result from the isomerisation of an initially formed normal replacement product (*i.e.*, cinnamyl acetate). It suggested therefore that in the amine replacement reactions dealt with in this paper the anomalous products (*e.g.*, XI, XIII, and XV) might be capable of rearrangement to the conjugated vinylacetylenic amines thus:

$$(XI.)\quad HC{\equiv}C\cdot CH(NEt_2)\cdot CH{=}CH\cdot CH_3 \longrightarrow HC{\equiv}C\cdot CH{=}CH\cdot CH(NEt_2)\cdot CH_3 \quad (XIX.)$$

provided that suitable conditions could be found. However with moderately concentrated acids the amine (XI) remains unaffected (under more vigorous conditions hydration of the acetylenic linkage tends to occur), suggesting that (XI) is indeed more stable than the conjugated isomer (XIX).

Note Added in Proof.—This suggestion is apparently borne out by the results of ethylation experiments with the secondary amine,

$$(IV.)\quad HC{\equiv}C\cdot CH{=}CH\cdot CH(NHEt)\cdot CH_3 \xrightarrow{EtBr} HC{\equiv}C\cdot CH(NEt_2)\cdot CH{=}CH\cdot CH_3 \quad (XI.)$$

2-ethylaminohex-3-en-5-yne (IV). Treatment with ethyl bromide at 80° gave, after removal of quaternary salt and unchanged secondary amine, a 30% yield of the unconjugated tertiary amine (XI). If the conjugated amine (XIX) is produced initially, as would normally be expected, it must undergo rearrangement under the conditions of the experiment to the apparently more stable unconjugated isomer (XI).

The only amine replacement reaction at all comparable with the present study is that carried out by Meisenheimer and Link (*loc. cit.*) with ethylaniline. Using equimolecular proportions of ethylaniline and cinnamyl chloride, a homogeneous product (*i.e.*, PhCH=CH·CH_2·NEtPh), involving no rearrangement, results. From the experiments described above, and also from related studies on the anionotropic rearrangement of phenylvinylcarbinol (Braude, Jones, and Stern, this vol., p. 396), only the normal product would be expected with the weak base employed and, in view of the low mobility of the phenylvinylcarbinol ⟶ cinnamyl alcohol system, it is unlikely that even diethylamine treatment of cinnamyl chloride would effect any appreciable rearrangement. It can be predicted, however, with a fair degree of certainty that styrylmethylcarbinyl chloride (PhCH=CH·CHCl·Me) should readily undergo rearrangement during amine replacements. It is hoped to examine these and allied reactions in the near future in the expectation of throwing further light on the relationship between both base strength and carbinol structure and the reaction mechanism.

Experimental.

Absorption spectra were determined in alcoholic solutions. Light petroleum refers to that fraction with b. p. 40—60° unless otherwise stated. The preparation of most of the chloro-compounds is described by Heilbron, Jones, Lacey, McCombie, and Raphael (*loc. cit.*).

2-*Anilinohex*-3-*en*-5-*yne* (V).—A solution of 2-chlorohex-3-en-5-yne (10 g.) in freshly distilled aniline (40 c.c.) was heated in a sealed tube at 100° for 16 hours. Much aniline hydrochloride separated. The mixture was treated with ether and 2N-sodium hydroxide, the aqueous portion was ether-extracted several times, and the combined ethereal solutions were washed with water, dried, and evaporated. After removal of aniline at 5 mm., a colourless oil (8·8 g.) was obtained, b. p. 85°/0·1 mm., $n_D^{19°}$ 1·5845. Cooling and trituration with light petroleum gave a solid product (5·5 g.) which on crystallisation from light petroleum gave 2-*anilinohex*-3-*en*-5-*yne* as prismatic needles, m. p. 57·5° (Found: C, 84·4; H, 7·65; N, 8·45. $C_{12}H_{13}N$ requires C, 84·2; H, 7·65; N, 8·2%). Active hydrogen (Zerewitinoff): The amine (47 mg.) evolved 12·8 c.c. of methane at 12°/768 mm., after heating to 90° (2·0 active hydrogen atoms per mol.).

A slow stream of dry hydrogen chloride was passed into a dry ethereal solution of the amine (0·3 g.). Scratching with a glass rod soon induced the separation of the derivative which was filtered off at intervals in order to avoid addition of hydrogen chloride to the ethylenic and acetylenic bonds. Crystallisation from acetone–light petroleum gave the *hydrochloride* (0·2 g.) as needles, m. p. 169° (Found: N, 6·95. $C_{12}H_{14}NCl$ requires N, 6·75%).

2-*Ethylaminohex*-3-*en*-5-*yne* (IV).—Prepared by heating ethylamine (90 c.c.) with 2-chlorohex-3-en-5-yne (19 g.) at 80° for 20 hours, followed by isolation in the manner described above, the *amine* (12·3 g.) was obtained with b. p. 72°/30 mm., $n_D^{13.5°}$ 1·4788 (Found: C, 77·85; H, 10·5. $C_8H_{13}N$ requires C, 78·0; H, 10·65%). Active hydrogen (Zerewitinoff): 50 Mg. gave 20·5 c.c. of methane at 20°/765 mm., after heating to 90° (18 c.c. after 1 hour at 20°) (2·1 active hydrogen atoms per mol.).

Prepared as described above from the amine (1 g.) in dry ether (30 c.c.) the *hydrochloride* separated from *iso*propyl alcohol–light petroleum as plates, m. p. 158° (Found: N, 8·7. $C_8H_{14}NCl$ requires N, 8·75%). The *α-naphthylurea*, obtained by adding α-naphthyl *iso*cyanate (0·3 g.) to a solution of the amine (0·3 g.) in petroleum (5 c.c.; b. p. 80—100°), crystallised from aqueous alcohol in needles, m. p. 127° (Found: N, 9·8. $C_{19}H_{20}ON_2$ requires N, 9·6%). Light absorption: Maximum, 2230A.; $\epsilon = 74{,}500$.

2-*Aminohex*-3-*en*-5-*yne* (III).—Heating the chloro-compound (30 g.) in liquid ammonia (250 c.c.) in an autoclave at 100° for 20 hours gave the primary *amine* (4·5 g.), b. p. 145°, 69—70°/39 mm., $n_D^{17°}$ 1·4934 (Found: C, 76·05; H, 9·65. C_6H_9N requires C, 75·75; H, 9·55%). Active hydrogen (Zerewitinoff): 24·5 Mg. gave 18 c.c. of methane at 18°/762 mm., after heating to 90° (12 c.c. after 1 hour at 18°) (2·95 active hydrogen atoms per mol.). The amine (0·3 g.) gave the *hydrochloride* which on crystallisation from alcohol–light petroleum (b. p. 60—80°) formed plates (0·2 g.), m. p. 171° (Found: N, 10·75. $C_6H_{10}NCl$ requires N, 10·65%). The *α-naphthylurea* crystallised from aqueous alcohol in plates, m. p. 168—169° (decomp.) (Found: N, 10·65. $C_{17}H_{16}ON_2$ requires N, 10·6%). Light absorption: Maxima, 2230 and 2195A.; $\epsilon = 58{,}000$ in each case. The *picrate* separated from ethyl acetate–light petroleum in yellow plates, m. p. 165° (Found: C, 44·65; H, 4·05. $C_{12}H_{12}O_7N_4$ requires C, 44·45; H, 3·75%).

1-*Diethylaminopent*-2-*en*-4-*yne* (VIII; R = H).—A mixture of 1-chloropent-2-en-4-yne (12 g.) and diethylamine (35 c.c.), heated at 80° for 16 hours (reaction occurs slowly in the cold) gave the *amine* (7·5 g.), b. p. 76°/27 mm., $n_D^{18°}$ 1·4730, as a colourless oil which rapidly becomes yellow in air (Found: C, 79·35, 79·65; H, 11·3, 11·3. $C_9H_{15}N$ requires C, 78·75; H, 11·05%). Active hydrogen (Zerewitinoff): 63 Mg. gave 11 c.c. of methane at 18°/749 mm., no increase after heating to 90° (1·0 active hydrogen atom per mol.). The *hydrochloride* formed plates, m. p. 172°, from chloroform–light petroleum (b. p. 60—80°) (Found: C, 62·25; H, 9·35. $C_9H_{16}NCl$ requires C, 62·25; H, 9·3%). The *picrate* crystallised from water in yellow needles, m. p. 124° (Found: C, 49·3; H, 4·8. $C_{15}H_{18}O_7N_4$ requires C, 49·15; H, 4·95%).

1-*Diethylaminonon*-2-*en*-4-*yne* (VIII; R = *n*-Bu).—1-Hexyne (86 g.) in dry ether (150 c.c.) was added to a solution of ethylmagnesium bromide (from Mg, 24 g.) and the well-agitated mixture was refluxed in nitrogen on a steam-bath for 1½ hours. The solution was cooled and acraldehyde (56 g.) in ether (200 c.c.) was added dropwise during 2½ hours, after which the solution was stirred at 20° for 16 hours. The Grignard complex was decomposed with ammonium nitrate and isolation with ether gave *non*-1-*en*-4-*yn*-3-*ol* (100 g.), b. p. 101—102°/21 mm., 94—95°/13 mm., $n_D^{20°}$ 1·4658 (Found: C, 78·25; H, 10·25. $C_9H_{14}O$ requires C, 78·15; H, 10·2%). Active hydrogen (Zerewitinoff): The carbinol (110 mg.) gave 18·0 c.c. of methane at 18°/761·5 mm. (0·95 active hydrogen atom per mol.). No light absorption with $E^{1\%}_{1cm.}$ >40 above 2200A.

The carbinol (12 g.) was shaken with concentrated hydrochloric acid (40 c.c.) at room temperature in nitrogen for 2 hours. Isolation of the product in the usual way gave 1-*chlorononn*-2-*en*-4-*yne* (10 g.), b. p. 105—108°/19 mm., $n_D^{21·5°}$ 1·4970 (Found: C, 69·3; H, 8·3. $C_9H_{13}Cl$ requires C, 69·0; H, 8·35%). Light absorption: Maximum, 2330A.; $\epsilon = 15{,}500$.

When the chloro-compound (10 g.) was mixed with diethylamine (30 c.c.), heat was evolved and diethylamine hydrochloride separated rapidly. After 20 hours' heating in a sealed tube at 90°, isolation of the basic product gave 1-*diethylaminonon*-2-*en*-4-*yne* (8·6 g.), b. p. 72—74°/4 mm., $n_D^{19°}$ 1·4800 (Found: C, 80·95; H, 11·75. $C_{13}H_{23}N$ requires C, 80·75; H, 12·0%). The hydrochloride, a crystalline solid, was too hygroscopic to be isolated in a pure condition.

4-*Diethylaminohex*-2-*en*-5-*yne* (XI).—Heating a mixture of 2-chlorohex-3-en-5-yne (40 g.) with diethylamine (130 c.c.) at 100° for 20 hours gave the *amine* (28 g.), b. p. 69°/19 mm., $n_D^{18°}$ 1·4568 (Found: C, 79·7; H, 11·1. $C_{10}H_{17}N$ requires C, 79·4; H, 11·35%). Active hydrogen (Zerewitinoff): 88 Mg. gave 13·8 c.c. of methane at 17°/766 mm., after heating to 90° (equivalent to 1·0 active hydrogen atom per mol.). Light absorption: End absorption at 2180A., $\epsilon = 2500$.

Treatment of the amine (5 g.) with hydrogen chloride as described above gave the ***hydrochloride*** (3 g.) as prisms, m. p. 144°, from either ethyl acetate–light petroleum (b. p. 60—80°) or *cyclo*hexanone–light petroleum (b. p. 60—80°) (Found: N, 7·6. $C_{16}H_{19}NCl$ requires N, 7·45%). It shows no absorption of appreciable intensity above 2200A. The ***methiodide***, prepared in ether at 20°, crystallised from acetone–light petroleum as irregular prisms, m. p. 117—118° (decomp.) (Found: C, 44·9; H, 6·8. $C_{11}H_{20}NI$ requires C, 45·05; H, 6·9%).

The base (2·1 g.) regenerated from the hydrochloride (2·7 g.) with 2N-sodium hydroxide had b. p. 68°/19 mm., $n_D^{19\cdot5°}$ 1·4552. Light absorption: End absorption only. At 2130A.; $\epsilon = 3000$.

4-Diethylaminodec-2-en-5-yne (XIII).—A mixture of 2-chlorodec-3-en-5-yne (11·5 g.) and diethylamine (20 c.c.) on heating at 100° for 20 hours gave the *amine* (10·5 g.), b. p. 70—71°/4 mm., $n_D^{18°}$ 1·4634 (Found: C, 80·9; H, 12·2. $C_{14}H_{25}N$ requires C, 81·05; H, 12·15%). It shows no absorption of $E^{1\%}_{1cm.}$ >100 above 2200A.

The *picrate*, prepared in acetone solution, was crystallised first from methyl alcohol and then from benzene–light petroleum (b. p. 60—80°), from which it separated as yellow prisms, m. p. 88° (Found: C, 54·25; H, 6·2. $C_{20}H_{28}O_7N_4$ requires C, 54·05; H, 6·45%).

4-Diethylamino-7-methylnona-2 : 7-dien-5-yne (XV).—2-Chloro-7-methylnona-2 : 7-dien-5-yne (9 g.) was heated with diethylamine (30 c.c.) at 95° for 20 hours in a stainless steel autoclave. Isolation of the basic material in the usual manner gave *4-diethylamino-7-methylnona-2 : 7-dien-5-yne* (6·5 g.), b. p. 57—59°/0·5 mm., $n_D^{19°}$ 1·4855 (Found: C, 82·15; H, 11·25. $C_{24}H_{29}N$ requires C, 81·9; H, 11·3%).

Ozonolysis of Propenylethynylcarbinol.—Ozonised oxygen (3%) was passed into a solution of the carbinol (0·96 g.) in "AnalaR" acetic acid (25 c.c.) at 15° through a fine capillary for twice the time theoretically required for the ozonolysis of the ethenoid linkage. The resulting solution was added dropwise during 15 minutes to a vigorously stirred mixture of zinc dust (10 g.) and boiling water (200 c.c.) to which small quantities of quinol and silver nitrate had been added. The mixture was then distilled in nitrogen, the distillate (about 60 c.c.), collected in a receiver at 0°, was neutralised (phenolphthalein) with dilute sodium hydroxide, and the resulting solution was redistilled, the distillate being passed into an excess of a saturated solution of dimedon in aqueous methanol (10%). The precipitate (1·45 g.) obtained after 24 hours had m. p. 135—138° and after crystallisation from aqueous alcohol yielded needles or plates of the dimedon derivative of acetaldehyde, m. p. 138—139°, undepressed on admixture with an authentic specimen (m. p. 140°).

Ozonolysis of 4-Diethylaminohex-2-en-5-yne (XI).—The amine (1·51 g.), ozonised as described above, gave acetaldehyde dimedon derivative (1·27 g.), m. p. 135—138°, which after one crystallisation from aqueous alcohol had m. p. 139°, undepressed on admixture with an authentic specimen.

Ozonolysis of 4-Diethylaminodec-2-en-5-yne (XIII).—The amine (2·07 g.), treated as indicated above, gave 1·06 g. of dimedon derivative, which softened at *ca.* 80° and had m. p. 105—120°. Crystallisation from pentane gave the acetaldehyde derivative (0·75 g.), m. p. 136—138° (mixed m. p. with authentic specimen, 138—140°). The more soluble, low m. p. impurity may have been the dimedon derivative (m. p. 105°) of *n*-valeraldehyde, arising from ozonolysis of the acetylenic bond.

Reactions of 2 : 9-Dichlorodeca-3 : 7-dien-5-yne (IX) *with Primary Amines.*—(*a*) A mixture of dry methylamine (20 g.) and 2 : 9-dichlorodeca-3 : 7-dien-5-yne (5 g.) was heated at 100° in a sealed tube for 24 hours. The clear liquid was treated with excess of concentrated hydrochloric acid and repeatedly extracted with ether until no more neutral material was extracted. The diamine was liberated from the acid solution with excess of sodium hydroxide solution and isolated by means of ether. Distillation then gave *2 : 9-bismethylaminodeca-3 : 7-dien-5-yne* (X) (2·6 g.), as a yellow liquid, b. p. 60° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·5371 (Found: C 75·0; H, 10·35. $C_{12}H_{20}N_2$ requires C 75·0; H, 10·5%).

(*b*) When the dichloro-compound (5 g.) was treated with ethylamine (20 g.) as described above the product consisted of *2 : 9-bisethylaminodeca-3 : 7-dien-5-yne* (2·5 g.), a pale yellow liquid, b. p. 116—118°/10^{-4} mm., $n_D^{18°}$ 1·5120 (Found: C, 76·5; H, 11·05. $C_{14}H_{24}N_2$ requires C, 76·3; H, 11·0%).

Reactions of 2 : 9-Dichlorodeca-3 : 7-dien-5-yne (IX) *with Secondary Amines.*—(*a*) The dichloro-compound (5 g.) was caused to react with diethylamine (20 g.) as described above, the reaction tube gradually becoming filled with crystals of diethylamine hydrochloride. The diamine mixture (6 g.; 90%) was isolated as a pale yellow liquid, b. p. 86—88°/10^{-3} mm., 110°/0·1 mm.; $n_D^{18°}$ 1·4890 (Found: C, 78·3; H, 11·4. Calc. for $C_{18}H_{32}N_2$: C, 78·2; H, 11·7%). Light absorption: Maximum, 2310A.; $\epsilon = 7500$. Redistillation of 3·5 g. of the mixture gave a product (2·5 g.) with $n_D^{17°}$ 1·4815. Light absorption: Maximum, 2200A.; $\epsilon = 5500$. Inflexion, 2420A.; $\epsilon = 4000$. Ozonolysis of this product (2·8 g.) followed by working up in the manner described above gave the dimedon derivative of acetaldehyde (0·9 g.), m. p. 139—140°, undepressed on admixture with an authentic sample.

(*b*) A mixture of the dichloro-compound (5 g.) and dimethylamine (20 g.) treated as above gave the diamine mixture (4·5 g.; 90%) as a yellow liquid, b. p. 50° (bath temp.)/10^{-4} mm., $n_D^{20°}$ 1·5146 (Found: C, 76·8; H, 10·75. Calc. for $C_{14}H_{24}N_2$: C, 76·3; H, 11·0%).

Note Added in Proof. Ethylation of 2-Ethylaminohex-3-en-5-yne (IV).—A mixture of the above amine (12·3 g.) and ethyl bromide (10·9 g.) together with a trace of quinol was heated at 80° for 48 hours. Isolation of the amine fraction gave 7 g. of material, b. p. 60—68°/15 mm., $n_D^{15°}$ 1·4615. This mixture, dissolved in petrol (20 c.c.; b. p. 100—120°), was treated with α-naphthyl *iso*cyanate until no further precipitate appeared to be formed. After 1 hour the solid was filtered off and on crystallisation from aqueous alcohol gave the α-naphthylurea of (IV) (3 g.), m. p. 127°, undepressed on admixture with an authentic sample. The petrol solution was shaken for some time with an excess of dilute hydrochloric acid, and the small amount of di-α-naphthylurea so formed was removed; treatment of the aqueous layer with alkali followed by isolation with ether gave 4-diethylaminohex-2-en-5-yne (XI) (4·5 g.), b. p. 63—65°/15 mm., $n_D^{14°}$ 1·4589. Light absorption in alcohol: End absorption only, $E^{1\%}_{1cm.}$ 90 at 2180A. The hydrochloride, after crystallisation from acetone–ethyl acetate, had m. p. 142—143°, undepressed on admixture with an authentic sample. It showed no absorption of appreciable intensity in the range 2200—4000A. The methiodide, crystallised once from acetone–light petroleum, had m. p. 115—117°, undepressed on admixture with an authentic sample.

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206. *Researches on Acetylenic Compounds. Part VIII. Miscellaneous Addition Reactions of Ethynyl Ketones.*

By Kenneth Bowden, Ernest A. Braude, and E. R. H. Jones.

In connexion with light-absorption studies (see following paper) a variety of addition reactions of the readily available ethynyl ketones (I) (Bowden, Heilbron, Jones, and Weedon, this vol., p. 39) mainly of the type indicated below (I ⟶ II), has been studied. The adducts employed include ammonia and amines, sulphinic acids, ethylthiol and thiophenol, alcohol and phenol, halogens, hydrogen bromide, and water.

In Part II (Bowden, Braude, Jones, and Weedon, this vol., p. 45) the facile addition of primary and secondary amines to ethynyl ketones (I) was described and, as a consequence of this study, a detailed survey of the auxochromic properties and conjugating power of the amino-group in substituted vinylamines became possible. The marked bathochromic and hyperchromic effects observed in the light-absorption behaviour of these nitrogen compounds suggested that the extension of this survey to include other elements was highly desirable. In partial pursuance of this new objective, addition reactions of ethynyl ketones (I) with sulphinic acids, ethylthiol and thiophenol, alcohol and phenol, halogens, hydrogen bromide, and water have now been studied, addition reactions which in general are of the type :

$$\text{(I.)}\quad R\cdot CO\cdot C{\equiv}CH + HX \longrightarrow R\cdot CO\cdot CH{=}CHX \quad \text{(II.)}$$

The light-absorption properties of the adducts (II), from which the auxochromic characteristics of the atom or group X can be ascertained, are reported in detail in the following paper. Certain data bearing upon stereochemical problems, however, are included below.

In order to render more complete our information concerning the light-absorption behaviour of substituted vinylamines, phenyl ethynyl ketone has been caused to react with diethylamine, ethylamine, and ammonia, *e.g.*,

$$Ph\cdot CO\cdot C{\equiv}CH + NH_3 \longrightarrow Ph\cdot CO\cdot CH{=}CH\cdot NH_2 \quad \text{(III.)}$$

In the last case, isomerism similar to that already encountered with other vinylamines (Bowden, Braude, Jones, and Weedon, *loc. cit.*) has been experienced. The crude product obtained by interaction of the ketone with liquid ammonia at its boiling point had m. p. 82°. Sublimation in a high vacuum yielded the *α-form* of *1-amino-3-phenylpropen-3-one* (III), m. p. 70°, and this on boiling with alcohol was extensively converted into the β-*form*, m. p. 90—91°. Both forms were practically unaffected by exposure in alcoholic solutions to ultra-violet light for a few minutes, and their light-absorption properties (cf. Part II, *loc. cit.*) are recorded below :

	M. p.	$\lambda_{max.}$, A.	$\epsilon_{max.}$		M. p.	$\lambda_{max.}$, A.	$\epsilon_{max.}$
(III)	70°	2420	14,000	(III)	90—91°	2420	11,000
		3240	22,000			3240	18,000

These results are somewhat similar to those already obtained with the isomers of 1-anilinobut-1-en-3-one (Me·CO·CH=CH·NHPh), although the intensity differences between the isomers of (III) are more clearly defined.

With many of the classical examples of geometrical isomerism it has been observed that the more stable, higher m. p. form (the *trans*-isomer) shows the more intense absorption (Henri and Errera, *Compt. rend.*, 1925, **180**, 2049; Castille, *Bull. Acad. roy. Belg.*, 1930, **16**, 81; cf. Koch, *Chem. and Ind.*, 1942, 273); notable exceptions, however, include the nitriles of crotonic and *iso*crotonic acids (Bruylants and Castille, *Bull. Acad. roy. Belg.*, 1927, **13**, 767) and the amides of geranic acid (Caldwell and Jones, this vol. p. 599). The light-absorption properties of the isomeric amines (III) are thus also exceptional when related to their melting points, as are the sulphones referred to later in this paper.

The preparation of 1-diethylaminohex-1-en-3-one ($Pr\cdot CO\cdot CH{=}CH\cdot NEt_2$) from propyl ethynyl ketone and diethylamine was reported in Part II (*loc. cit.*) and it seemed desirable to complete the series of aliphatic vinylamines by the reaction of this ethynyl ketone with both ethylamine and ammonia. In the former case *1-ethylaminohex-1-en-3-one* was readily isolated, but with liquid ammonia only a poor yield of a highly unstable substance, which failed to show the expected light-absorption properties, was obtained.

The addition of a sulphinic acid to the triple bond of a substituted αβ-acetylenic ketone has been described by Kohler and Barrett (*J. Amer. Chem. Soc.*, 1924, **46**, 748) who treated benzoylphenylacetylene ($Ph\cdot CO\cdot C{\equiv}C\cdot Ph$) with *p*-toluenesulphinic acid, obtaining two stereoisomeric sulphones. Phenyl ethynyl ketone has been found to react smoothly with this acid in alcoholic solution giving two isomeric *sulphones* of structure (IV). Kohler

$$p\text{-}Me\cdot C_6H_4\cdot SO_2H + HC{\equiv}C\cdot CO\cdot Ph \longrightarrow p\text{-}Me\cdot C_6H_4\cdot SO_2\cdot CH{=}CH\cdot CO\cdot Ph \quad \text{(IV.)}$$

and Larsen (*ibid.*, 1935, **57**, 1448) prepared the sulphone, $Ph\cdot SO_2\cdot CH{=}CH\cdot CO\cdot Ph$, in stereoisomeric forms, by a roundabout route. A mixture of the isomers, which can be resolved by crystallisation, is readily obtained by interaction of benzenesulphinic acid and phenyl ethynyl ketone and, as was shown by Kohler and Larsen (*loc. cit.*), the form with m. p. 113—115° is converted into the other form (m. p. 148—149°) by irradiation with ultra-violet light, the reverse change being catalysed by traces of hydrogen chloride or sodium methoxide.

$$Ph\cdot SO_2\cdot CH{=}CH\cdot CO\cdot Ph,\ \text{m. p. 113—115°}\ (\text{"}\textit{trans}\text{"}) \xrightarrow[\text{HCl or NaOMe}]{h\nu} \text{m. p. 148—149°}\ (\text{"}\textit{cis}\text{"})$$

In the classical cases of geometrical isomerism the more unstable, lower melting *cis*-forms (*e.g.*, maleic acid) are usually produced from the more stable, higher melting *trans*-forms (*e.g.*, fumaric acid) by irradiation, the reverse conversion being effected in the presence of halogens, halogen acids, etc., at ordinary temperatures. Kohler and Larsen (*loc. cit.*) therefore suggested that, in spite of the melting-point indications, the lower m. p. sulphone had the *trans*-configuration. On the same basis the lower m. p. form of the tolyl sulphone (IV) can also be assigned a *trans*-configuration. The light-absorption data for these four substances (in alcoholic solutions) are indicated below.

	"*cis*"			"*trans*"		
Sulphone.	M. p.	$\lambda_{max.}$, A.	$\epsilon_{max.}$	M. p.	$\lambda_{max.}$, A.	$\epsilon_{max.}$
$Ph{\cdot}SO_2{\cdot}CH{=}CH{\cdot}CO{\cdot}Ph$	148—149°	2370	16,000	113—115°	2280	12,000
		2420	16,000		2450	13,000
		2480	16,000		2510	13,500
		2510	16,000		2570	16,500
		2800	4,000		2650	16,500
					2800	11,500
					2900	9,500
p-$Me{\cdot}C_6H_4{\cdot}SO_2{\cdot}CH{=}CH{\cdot}CO{\cdot}Ph$	129	2450	29,000	98	2510	16,500
		2520	27,000		2560	16,500
		2800	7,000		2800	12,000

It will be noted that, in agreement with the suggestion of Kohler and Larsen (*loc. cit.*), the so-called *trans*-forms absorb at 2800 A. (the shorter wave-length absorption is probably due to the partial chromophore $Ph{\cdot}CO{\cdot}CH{=}CH$) with appreciably greater intensities than the *cis*-forms (see above). The marked diminution in fine structure, consequent upon the introduction of the methyl group into the benzene nucleus, is well illustrated in the above examples.

Although thiophenol has been combined with phenylacetylene (Kohler and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316), little work seems to have been done on addition reactions with acetylenic ketones. By using

$$PhSH + HC{\equiv}C{\cdot}CO{\cdot}Ph \longrightarrow PhS{\cdot}CH{=}CH{\cdot}CO{\cdot}Ph \qquad (V.)$$

piperidine (cf. Ruhemann, *J.*, 1905, **87**, 467) or sodium methoxide as catalysts, good yields of vinyl sulphides (*e.g.*, V) are obtainable when thiophenol and ethylthiol react with ethynyl ketones.

Reactions with phenols in the presence of sodium phenoxide (cf. Moureu and Brachin, *Bull. Soc. chim.*, 1905, **33**, 134) take a similar course, vinyl ethers, *e.g.*, $PhO{\cdot}CH{=}CH{\cdot}CO{\cdot}Ph$, being formed in good yields. The employment of alcohols in such addition reactions with ethynyl ketones, on the other hand, leads to unexpected results. With substituted acetylenic ketones of type (VI), where R and R_1 are aryl groups, β-alkoxyvinyl

$$(VI.) \quad R{\cdot}CO{\cdot}C{\equiv}CR_1 + EtOH \longrightarrow R{\cdot}CO{\cdot}CH{=}CR_1{\cdot}OEt \quad (VII.)$$

ketones (*e.g.*, VII) are usually formed as the result of mono-addition (cf. Claisen, *Ber.*, 1903, **36**, 3665; 1911, **44**, 1165; Viguier, *Ann. Chim.*, 1913, **28**, 503; Weygand, *Ber.*, 1925, **58**, 1478; Moureu and Brachin, *Bull. Soc. chim.*, 1922, **31**, 1299). When phenyl ethynyl ketone is treated with alcohol and sodium ethoxide, the *di-adduct* (VIII), with light absorption properties ($\lambda_{max.}$ 2390, 2420 A., $\epsilon_{max.}$ 15,000 and 15,000) similar to those of

$$Ph{\cdot}CO{\cdot}C{\equiv}CH + 2EtOH \longrightarrow Ph{\cdot}CO{\cdot}CH_2{\cdot}CH(OEt)_2 \qquad (VIII.)$$

acetophenone [$\lambda_{max.}$ 2400 A.; $\epsilon_{max.}$ 13,000 (Ley and Wingchen, *Ber.*, 1934, **67**, 501)] is obtained. In the same way propyl ethynyl ketone gives the *diethoxy-ketone* (IX) and the *triethoxyhexanone* (X) is isolated from

$$(IX.) \quad CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH(OEt)_2 \qquad CH_3{\cdot}CH(OEt){\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH(OEt)_2 \quad (X.)$$

propenyl ethynyl ketone. Purification of (IX) and (X) is rendered extremely difficult by their persistent contamination with small quantities of unsaturated ketones which are not easily eliminated by fractional distillation. Moureu and Lazennac (*Bull. Soc. chim.*, 1906, **35**, 528) found that by the interaction of αβ-acetylenic nitriles with methyl alcohol and sodium methoxide inseparable mixtures of mono- and di-adducts were produced, but when potassium hydroxide was employed as catalyst only mono-addition occurred. Even in the presence of potassium hydroxide, however, only di-adducts can be obtained from the ethynyl ketones. Attempts to split off alcohol from these di-adducts by heating with *p*-toluenesulphonic acid (cf. Killian, Hennion, and Nieuwland, *J. Amer. Chem. Soc.*, 1935, **57**, 544; Nazarov, *Bull. acad. sci. U.R.S.S.*, 1940, 545) results in extensive decomposition. It would appear that the presence of the ethynyl hydrogen atom is an important factor in stabilising these di-adducts in the acetal form.

The addition of bromine to ethynyl ketones (cf. Grard, *Ann. Chim.*, 1930, **13**, 363; Dufraisse, *ibid.*, 1922, **17**, 141, who employed substituted acetylenic ketones) proceeds smoothly at 15—20° in chloroform solution. Judging from the wide b. p. range and variations in refractive indices, the *dibromide* from propyl ethynyl ketone is a mixture of the two possible stereoisomerides. Addition of chlorine to the same ketone gave a product boiling over a wide range and, although an arbitrary cut had the anticipated light-absorption properties, satisfactory analytical data could not be obtained. The reaction of propyl ethynyl ketone with hydrogen bromide in acetic acid solution gave the somewhat unstable 1-*bromohexen*-3-*one*.

Many examples of the hydration of substituted acetylenic ketones to β-diketones are to be found in the literature. Nef (*Annalen*, 1899, **308**, 277) obtained dibenzoylmethane by treating benzoylphenylacetylene with concentrated sulphuric acid, and this method has been employed by a number of other workers (Yvon, *Compt. rend.*, 1925, **180**, 748; Moureu and Delange, *Bull. Soc. chim.*, 1901, **25**, 306; *Ann. Chim.*, 1914, **2**, 277; Fuson, Ullyot, and Huckson, *J. Amer. Chem. Soc.*, 1939, **61**, 410; Morton, Hassan, and Calloway, *J.*, 1934, 899). Phenyl ethynyl ketone remains unchanged after dissolution in concentrated sulphuric acid at 20° followed by dilution with water, and at higher temperatures decomposition occurs. However, with dilute sulphuric acid containing mercuric sulphate at 80—100°, hydration occurs smoothly giving 1-phenylpropane-

$$Ph{\cdot}CO{\cdot}C{\equiv}CH \longrightarrow Ph{\cdot}CO{\cdot}CO{\cdot}CH_3 \qquad (XI.)$$

1 : 2-dione (XI), characterised as its α-semicarbazone. Thus, in common with all compounds containing the ethynyl group, and in spite of the presence of the α-carbonyl group, hydration of the triple bond results in the formation of a ketone and not an aldehyde.

Experimental.

(The preparation of the ethynyl ketones is described by Bowden, Heilbron, Jones, and Weedon, this vol., p. 39.)

1-*Amino*-3-*phenylpropen*-3-*one* (III).—Finely powdered phenyl ethynyl ketone (1 g.) was added during 5 minutes to boiling liquid ammonia (25 c.c.), care being taken to exclude moisture. The solvent was then allowed to evaporate during an hour, and removal of the last traces under diminished pressure gave a pale yellow solid (1·1 g.), m. p. 82°. Sublimation at 50° (bath temp.)/10^{-4} mm. gave the *α-form* of 1-*amino*-3-*phenylpropen*-3-*one* (0·9 g.) as colourless needles, m. p. 70° (Found : N, 9·35. C_9H_9ON requires N, 9·5%). The *picrate*, prepared in methanol, crystallised from alcohol in long yellow needles, m. p. 174—175° (Found : N, 15·1. $C_{15}H_{12}O_8N_4$ requires N, 14·9%).

The *β-form* was prepared by refluxing the α-form in alcohol for 10 minutes, removing the solvent under reduced pressure, and washing the residual solid with cold ether. It forms rosettes of needles, m. p. 90—91° (Found : N, 9·35%).

1-*Ethylamino*-3-*phenylpropen*-3-*one*.—Phenyl ethynyl ketone (6·5 g.) in ether (25 c.c.) was treated at 0° with ethylamine (4 c.c.) in ether (25 c.c.). Next day the solvent was evaporated, and distillation gave 1-*ethylamino*-3-*phenylpropen*-3-*one* (6·5 g.), b. p. 109°/0·4 mm. (Found : C, 75·6; H, 7·6. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5%).

1-*Diethylamino*-3-*phenylpropen*-3-*one*.—Prepared from the ketone (6·5 g.) and diethylamine (5·5 g.) in ether (40 c.c.) at 20—30°. Distillation gave an oil (8·1 g.), b. p. 147°/0·5 mm., which solidified, and crystallisation from light petroleum (b. p. 40—60°) gave the *amino-ketone* (7·5 g.) as pale yellow needles, m. p. 52—53° (Found : C, 77·2; H, 8·65. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4%).

1-*Ethylaminohex*-1-*en*-3-*one*.—The *amino-ketone* (3·5 g.) prepared by interaction of propyl ethynyl ketone (3·2 g.) with ethylamine (1·5 g.) in ether (20 c.c.) at 20° had b. p. 114—115°/20 mm., $n_D^{17°}$ 1·5236 (Found : N, 9·7. $C_8H_{15}ON$ requires N, 9·9%).

1-p-*Toluenesulphonyl*-3-*phenylpropen*-3-*one* (IV).—A solution of phenyl ethynyl ketone (2·6 g.) in alcohol (40 c.c.) was heated with *p*-toluenesulphinic acid (3·6 g.) on a steam-bath for 10 minutes. The solid separating on cooling was crystallised from alcohol and gave the *α-form* of 1-p-*toluenesulphonyl*-3-*phenylpropen*-3-*one* (5·1 g.) as needles, m. p. 129° (Found : C, 67·25; H, 5·2. $C_{16}H_{14}O_3S$ requires C, 67·1; H, 4·95%).

From the filtrates, by crystallisation from aqueous methanol, the *β-form* (0·5 g.) was obtained as long needles, m. p. 98—99° (Found : C, 67·1; H, 5·1%).

1-*Benzenesulphonyl*-3-*phenylpropen*-3-*one*.—The ketone (2·6 g.) and benzenesulphinic acid (3·2 g.) were heated in alcohol (40 c.c.) for 10 minutes on a steam-bath. After an hour at 0° the crystals (2·8 g., m. p. 146—148°) which separated were filtered off and crystallised from methanol giving "*cis*"-1-benzenesulphonyl-3-phenylpropen-3-one (2·05 g.), m. p. 148—149° (Kohler and Larsen, *loc. cit.*, give m. p. 149°).

The solid obtained from the mother liquors was crystallised from methanol giving the "*trans*"-form, m. p. 113—115° (Kohler and Larsen, *loc. cit.*, give m. p. 114°). This "*trans*"-form was also prepared from the "*cis*"-form by refluxing for 20 minutes in methanol containing a trace of alkoxide.

1-*Phenylthio*-3-*phenylpropen*-3-*one* (V).—Thiophenol (2·2 g.) in ether (10 c.c.) to which three drops of piperidine had been added was dropped into phenyl ethynyl ketone (2·6 g.) in ether (10 c.c.) at 20° during 15 minutes. Removal of the solvent and crystallisation from petroleum (b. p. 80—100°) gave 1-*phenylthio*-3-*phenylpropen*-3-*one* (4·6 g.) as pale yellow needles, m. p. 82—83° (Found : C, 74·85; H, 4·95. $C_{15}H_{12}OS$ requires C, 75·0; H, 5·05%).

1-*Ethylthio*-3-*phenylpropen*-3-*one*.—Ethylthiol (4 c.c.) in ether (15 c.c.) was caused to react with phenyl ethynyl ketone (6·5 c.c.) in ether (25 c.c.) at 20—30°, using a trace of sodium methoxide as catalyst. Distillation of the residue obtained after removal of the solvent gave 1-*ethylthio*-3-*phenylpropen*-3-*one* (6·5 g.), b. p. 125—126°/0·5 mm. (Found : C, 69·0; H, 6·65. $C_{11}H_{12}OS$ requires C, 68·7; H, 6·3%).

1-*Ethylthiohex*-1-*en*-3-*one*.—Ethylthiol (7·5 c.c.) in ether (50 c.c.) was added dropwise to propyl ethynyl ketone (9·6 g.) in ether (50 c.c.) to which a trace of sodium methoxide had previously been added. After the addition, carried out at 20°, was complete, the mixture was kept for 12 hours. Evaporation and distillation gave 1-*ethylthiohex*-1-*en*-3-*one* (10 g.), b. p. 130—131°/20 mm., $n_D^{20°}$ 1·5288 (Found : C, 60·45; H, 8·9. $C_8H_{14}OS$ requires C, 60·7; H, 8·9%).

1-*Phenoxy*-3-*phenylpropen*-3-*one*.—A solution of sodium phenoxide was prepared from sodium (1·15 g.) and molten phenol (50 g.), and phenyl ethynyl ketone (6·5 g.) was added in portions at 80°. During the addition the temperature rose to 90° and the mixture darkened. After cooling, the product was isolated with ether giving a pale yellow oil (9 g.), b. p. 150—155°/0·5 mm. Redistillation at 90° (bath temp.)/10^{-4} mm. gave a solid (6·9 g.), m. p. 46—48°, which after crystallisation from light petroleum (b. p. 60—80°) gave 1-*phenoxy*-3-*phenylpropen*-3-*one* (4 g.), m. p. 49·5—50·5° (Found : C, 80·4; H, 5·45. $C_{15}H_{12}O_2$ requires C, 80·35; H, 5·4%). A small quantity of material, m. p. 27—29°, presumably a stereoisomer, was also isolated.

1 : 1-*Diethoxy*-3-*phenylpropan*-3-*one* (VIII).—To a solution of sodium ethoxide, prepared from sodium (1·15 g.) and alcohol (50 c.c.), phenyl ethynyl ketone (6·5 g.) in alcohol (25 c.c.) was added with stirring during 1 hour, the temperature being kept at 0—5°. After acidification with acetic acid (3 g.), isolation by means of ether gave 1 : 1-*diethoxy*-3-*phenylpropan*-3-*one* (7·9 g.), b. p. 111—112°/1 mm., $n_D^{18°}$ 1·5032 (Found : C, 70·55; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·15%).

1 : 1-*Diethoxyhexan*-3-*one* (IX).—(*a*) Propyl ethynyl ketone (9·6 g.) in alcohol (50 c.c.) was added at 0—5° with stirring during 90 minutes to a solution of sodium (2·3 g.) in alcohol (100 c.c.). After a further 30 minutes the mixture was acidified with acetic acid; isolation with ether gave, after prolonged fractionation, 1 : 1-*diethoxyhexan*-3-*one* (10 g.), b. p. 96°/10 mm., $n_D^{19·5°}$ 1·4211 (Found : C, 64·05; H, 10·85. $C_{10}H_{20}O_3$ requires C, 63·75; H, 10·7%). The urethane

derivative was prepared from the diethoxy-ketone (1·5 g.) by stirring with urethane (5 g.) dissolved in N-hydrochloric acid (50 c.c.) at 20°. The sparingly soluble product crystallised from water in long needles (1·1 g.), m. p. 133—134° (Found: N, 10·0. $C_{12}H_{22}O_5N_2$ requires N, 10·2%).

(*b*) To a solution of potassium hydroxide (11·2 g.) in alcohol (90 c.c.), kept at 0—5°, propyl ethynyl ketone (9·6 g.) in alcohol (20 c.c.) was added with stirring during 30 minutes. The deep red solution was stirred for a further 30 minutes, and after acidification with acetic acid the product was isolated by means of ether. This procedure gave after repeated fractionation 1 : 1-diethoxyhexan-3-one (7 g.), b. p. 98—99°/14 mm., $n_D^{14.5°}$ 1·4250.

1 : 1 : 5-*Triethoxyhexan-3-one* (X).—To a solution of sodium (4·6 g.) in alcohol (200 c.c.) kept at 0—5°, propenyl ethynyl ketone (18·8 g.) in alcohol (50 c.c.) was added with stirring during 30 minutes. The mixture was then acidified with acetic acid; isolation with ether gave 1 : 1 : 5-*triethoxyhexan-3-one* (21·4 g.), b. p. 74—75°/0·3 mm., $n_D^{18.5°}$ 1·4279 (Found: C, 62·7, 62·7; H, 10·15, 10·55. $C_{12}H_{24}O_4$ requires C, 62·05; H, 10·4%).

1-*Bromohex-1-en-3-one*.—A solution of hydrogen bromide in acetic acid (16·2 c.c.; 50% w/v) was added to propyl ethynyl ketone (9·6 g.) in acetic acid (20 c.c.) at 5—10°. After dilution with water, isolation with chloroform gave 1-*bromohex-1-en-3-one* (4·7 g.), b. p. 80°/18 mm., $n_D^{16°}$ 1·5021 (Found: Br, 45·35. C_6H_9OBr requires Br, 45·15%). The ketone rapidly decomposes and it assumes a red colour after being kept for 30 minutes at 0°.

1 : 2-*Dibromohex-1-en-3-one*.—Bromine in chloroform (80 g.; 20% w/w) was added during 30 minutes to propyl ethynyl ketone (9·6 g.) in chloroform (25 c.c.) at such a rate that any appreciable excess of free bromine was avoided. The 1 : 2-*dibromohex-1-en-3-one* (20 g.) had b. p. 102—108°/17 mm., and $n_D^{18°}$ (of the various fractions) 1·5282—1·5365. After two fractionations a middle cut, b. p. 104·5—105°/17 mm., $n_D^{17°}$ 1·5340 was taken and used for analysis (Found: Br, 62·45. $C_6H_8OBr_2$ requires Br, 62·45%). The 2 : 4-*dinitrophenylhydrazone* formed bright yellow leaflets, m. p. 176°, from ethyl acetate (Found: N, 12·8. $C_{12}H_{12}O_4N_4Br_2$ requires N, 12·85%). Light absorption in chloroform: Maxima, 2560, 2820, 2900, 3650 A.; ϵ = 13,500, 10,500, 8000, and 25,500 respectively.

1-*Phenylpropane*-1 : 2-*dione* (XI).—2N-Sulphuric acid (50 c.c.) containing mercuric sulphate (0·25 g.) was added to phenyl ethynyl ketone (6·5 g.) in alcohol (100 c.c.). The mixture was stirred under reflux on a steam-bath for 6 hours, a further quantity of mercuric sulphate (0·25 g.) in 2N-sulphuric acid (50 c.c.) being added in portions during this time. Isolation with ether gave 1-phenylpropane-1 : 2-dione (4·1 g.) as a yellow oil, b. p. 88°/17 mm., $n_D^{17°}$ 1·5350 (von Auwers, *Ber.*, 1918, **51**, 1122, gives $n_D^{19°}$ 1·537). The *a*-semicarbazone crystallised from alcohol in leaflets, m. p. 208° (von Auwers and Ludewig, *Annalen*, 1936, **526**, 130, give m. p. 208—209°).

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207. *Studies in Light Absorption. Part III. Auxochromic Properties and the Periodic System.*

By KENNETH BOWDEN, ERNEST A. BRAUDE, and E. R. H. JONES.

Existing and new data are collected and discussed concerning the effects of covalently saturated substituents on the ultra-violet light absorption of unsaturated systems. It is shown that the observed bathochromic effects ($\Delta\lambda_X$) are even larger in acyclic ethylenic than in aromatic compounds. They are dependent on the nature of the ethylenic system, increasing with increasing polarisability and electronic mobility of the latter, in the order X·Ph < X·C=C < X·C=C·C=C < X·C=C·C=O, where X = CR_3, SiR_3, NR_2, OR, SR, or Hal. (R = H or alkyl.) $\Delta\lambda_X$ bears a definite relationship to the position of the substituent element in the periodic system, reaching a maximum with nitrogen amongst the non-metals of the first period, and increasing on ascending a group; there is thus a pronounced parallelism between the auxochromic effects of substituents and their tautomeric effects on chemical reactivity. Hypsochromic effects are observed when the substituent forms part of certain heterocyclic rings or when it is linked directly to a carbonyl chromophore, *e.g.*, in X·C=O and X·C(=O)·C=C.

IT has long been recognised that the substitution of certain groups (" auxochromes ") for hydrogen atoms directly attached to covalently unsaturated systems exhibiting selective light absorption in the visible region of the spectrum results in increases in the wave-lengths and intensities of the maxima (" batho- and hyperchromic " effects). The most effective auxochromes, in the classical sense, are groups themselves covalently unsaturated (*e.g.*, $-C{=}C-$, $-C{=}N-$, $-NO_2$), but the colour of dyes is also deepened and intensified by certain suitably positioned covalently saturated substituents (*e.g.*, $-NR_2$, $-OR$, $-SR$), that is, co-ordinatively unsaturated groups containing unshared electron pairs. Similar phenomena are well known in connection with the ultra-violet light absorption of aromatic systems, but aliphatic compounds have only recently been examined from this point of view. It has been shown that amino-substituents in aliphatic ethylenic systems give rise to large batho- and hyper-chromic effects (Bowden, Braude, Jones, and Weedon, this vol., p. 45), and it had previously been observed that alkyl groups which are neither covalently nor co-ordinatively unsaturated also produce small, but definite, bathochromic displacements (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1318; Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76; Gillam *et al.*, *J.*, 1940, 1453; 1941, 1123; 1943, 565; 1945, 432; Braude and Jones, *J.*, 1945, 498; Carr and Stücklen, *Z. physikal. Chem.*, 1934, *B*, 25, 57; Carr, Pickett, and Stücklen, *Rev. Mod. Physics*, 1942, **14**, 260; Price, *Ann. Reports*, 1939, **36**, 47).

In the present communication existing and new data are collected which illustrate the variochromic effects of vicinal carbon, silicon, nitrogen, oxygen, sulphur, chlorine, and bromine substituents in unsaturated aliphatic systems. It is shown that these effects are more marked than those observed in aromatic and heterocyclic compounds and that they can be correlated with the position of the substituent element in the periodic system.

The data in Table I refer to substituents attached to an ethylenic group, the latter being either isolated or

TABLE I.

The Auxochromic Effects of Substituents in Ethylenic Systems.

Auxochrome.	Unsubstituted compound.	$\lambda_{max.}$, A.	$\epsilon_{max.}$ ($\times 10^{-3}$).	Substituted compound.	$\lambda_{max.}$, A.	$\epsilon_{max.}$ ($\times 10^{-3}$).	$\Delta\lambda$.	$\Delta\epsilon$ ($\times 10^{-3}$).	Solvent.	Refs.
	$CH_2{=}CH{\cdot}CH{=}CH_2$	2170	21	$\mathbf{C}H_3{\cdot}CH{=}CH{\cdot}CH{=}CH_2$	2240	26	70	5	H	1
	,,	2170	21	$CH_2{=}C(\mathbf{C}H_3){\cdot}CH{=}CH_2$	2200	24	30	3	H	1
	,,	2170	21	$\mathbf{C}H_3{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}\mathbf{C}H_3$	2270	23	100	2	H	1
$-CH_3$	$CHMe(OH){\cdot}CH{=}CH{\cdot}C{\equiv}CH$	2230	13	$CHMe(OH){\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}\mathbf{Bu}^{\alpha}$	2280	16	50	3	A	2
	$CH_2{=}CH{\cdot}CMe{=}O$	2100	7	$\mathbf{C}H_3{\cdot}CH{=}CH{\cdot}CMe{=}O$	2240	10	140	3	A	1, 3
	,,	2100	7	$CH_2{=}C(\mathbf{C}H_3){\cdot}CMe{=}O$	2180	8	80	1	A	1, 3
	,,	2100	7	$\mathbf{C}H_3{\cdot}CH{=}C(\mathbf{C}H_3){\cdot}CMe{=}O$	2300	11	200	4	A	1, 3
$-SiR_3$	$CHMe{=}CMe{\cdot}C{\equiv}CH$	2190	9	$CHMe{=}CMe{\cdot}C{-}C{\cdot}\mathbf{Si}Et_3$	2340	15	150	6	H	3
	$CHBu^{\alpha}{=}CHEt$	1850	8	$C_5H_{10}\mathbf{N}{\cdot}CH{=}C(Et)$†	2280	10	430	2	H	4, 5
	$CH_2{=}CH{\cdot}CH{=}CH_2$	2170	21	$Et_2\mathbf{N}{\cdot}CH{=}CH{\cdot}CH{=}CH_2$	2810	24	640	3	H	1, 5
$-NR_2$	$CHMe{=}CH{\cdot}CO_2Et$	2070 *	20	$Et_2\mathbf{N}{\cdot}CMe{=}CH{\cdot}CO_2Et$	2880	31	810	11	A	8, 5
	$CH_2{=}CH{\cdot}CPr^{\alpha}{=}O$	2140	8	$Et_2\mathbf{N}{\cdot}CH{=}CH{\cdot}CPr^{\alpha}{=}O$	3070	28	930	20	A	7, 5
	$CH_2{=}CH{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}Ph$	2480	11	$Et_2\mathbf{N}{\cdot}CH{=}CH{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}Ph$	3430	25	950	14	A	5
	$CHMe{=}CH{\cdot}CO_2H$	2040	10	$MeO{\cdot}CMe{=}CH{\cdot}CO_2H$	2340	14	300	4	A	8, 3
$-OR$	,,	2040	10	$CHMe{=}C(OMe){\cdot}CO_2H$	2230	9	190	−1	A	8, 3
	$CHMe{=}CH{\cdot}CMe{=}O$	2170	10	$HO{\cdot}CMe{=}CH{\cdot}CMe{=}O$	2690	12	520	2	H	1, 6
	$CHBu^{\alpha}{=}CHEt$	1850	8	$Cl(CH_2)_2\mathbf{S}{\cdot}CH{=}CH_2$	2280	7	430	−1	H	4, 3
$-SR$	$CH_2{=}CH{\cdot}CPr^{\alpha}{=}O$	2070 *	8	$Et\mathbf{S}{\cdot}CH{=}CH{\cdot}CPr^{\alpha}{=}O$	2920	15	850	7	H	7, 3
	$CH_2{=}CH{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}Ph$	2480	11	$Et\mathbf{S}{\cdot}CH{=}CH{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}Ph$	3190	18	710	7	A	7, 3
	$CH_2{=}CH_2$	1750	?	$\mathbf{Cl}{\cdot}CH{=}CH_2$	1850	?	100	?	V	9
	$CH_2{=}CH{\cdot}CH{=}CH_2$	2170	21	$CH_2{=}C(\mathbf{Cl}){\cdot}CH{=}CH_2$	2230	14	60	−7	H	1, 3
$-Cl$	$CHMe{=}CH{\cdot}CO_2H$	2040	10	$CHMe{=}C(\mathbf{Cl}){\cdot}CO_2H$	2220	11	180	1	A	8, 3
	$CH_2{=}CH{\cdot}CMe{=}O$	2100	7	$\mathbf{Cl}{\cdot}CH{=}CH{\cdot}CMe{=}O$	2280	10	180	3	A	3
	$CH_2{=}CH{\cdot}CPr^{\alpha}{=}O$	2070 *	8	$\mathbf{Cl}{\cdot}CH{=}C(\mathbf{Cl}){\cdot}CPr^{\alpha}{=}O$	2480	6	410	−2	H	7, 3
	$CHMe{=}CH{\cdot}CO_2H$	2040	10	$CHMe{=}C(\mathbf{Br}){\cdot}CO_2H$	2280	7	240	−3	A	8, 3
$-Br$	$CH_2{=}CH{\cdot}CPr^{\alpha}{=}O$	2070 *	8	$\mathbf{Br}{\cdot}CH{=}CH{\cdot}CPr^{\alpha}{=}O$	2370	5	300	−3	H	7, 3
	,,	2070 *	8	$\mathbf{Br}{\cdot}CH{=}C(\mathbf{Br}){\cdot}CPr^{\alpha}{=}O$	2590	7	520	−1	H	7, 3

H = *n*-hexane solution, A = ethanol solution, V = vapour. † $C_5H_{10}N$ = piperidyl.

* Calculated empirically, assuming $\lambda_{max.}$ (ethanol) − $\lambda_{max.}$ (hexane) = 70 A. (cf. Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; Evans and Gillam, *J.*, 1945, 432).

[1] Booker, Evans, and Gillam, *J.*, 1940, 1453; Evans and Gillam, *J.*, 1941, 815. [2] Jones and McCombie, *J.*, 1943, 261; Heilbron, Jones, and Raphael, *J.*, 1943, 264. [3] This paper. [4] Platt, Rusoff, and Klevens, *J. Chem. Physics*, 1943, **11**, 535. [5] Bowden, Braude, Jones, and Weedon, this vol., p. 45. [6] Grossmann, *Z. physikal. Chem.*, 1924, **109**, 305. [7] Bowden, Heilbron, Jones, and Weedon, this vol., p. 39. [8] Mohler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485. [9] Price and Tutte, *Proc. Roy. Soc.*, 1940, *A*, **174**, 207.

itself conjugated with another ethylenic or with an acetylenic, carbonyl, or carboxyl group. As far as possible, the compounds chosen to represent the various systems were the simplest of their class, but, where the necessary data were not available, similarly substituted reference compounds have been employed. The bathochromic effects deduced for the elements Si, N, O, and S refer to substituents SiR_3, NR_2, OR, and SR (where R = alkyl), and although the bathochromic effects of alkyl groups and the chromolatory (transmitting) capacities of auxochromes are in any case small, the values will, nevertheless, be slightly larger (*ca.* 50—100 A.) than those appertaining to the simple SiH_3, NH_2, OH, and SH substituents.

From the data in Table I, a number of generalisations clearly emerge. These may be summarised as follows:

(i) Substituents attached to an ethylenic linkage which may either be isolated or form part of a conjugated system increase $\lambda_{max.}$ and usually $\epsilon_{max.}$.

(ii) The bathochromic effects depend primarily on the nature of the element vicinal to the ethylenic group, varying in the order C < Si, O < S, Cl < Br, and C < N > O > Cl, *i.e.*, increasing on ascending a group of the periodic system, and reaching a maximum with nitrogen in the first period (see also Table I*a*).

(iii) The effect of any one substituent also depends on the nature of the conjugated ethylenic system to which it is attached, increasing in the order X·C=C < X·C=C·C=C < X·C=C·C<O,O < X·C=C·C=O (see also Table I*a*).

(iv) Substituents in conjugated ethylenic systems produce larger bathochromic effects when they are located at the end of the system than when they are "cross-conjugated."

(v) The effects of two and more substituents are roughly additive.

TABLE I*a*.

Summary of Bathochromic Effects ($\Delta\lambda_X$, A.) *of Substituents* (*X*) *in Ethylenic Systems* (*R* = *alkyl group*).

	Substituent X.						
Substituted system.	CH_3.	SiR_3.	NR_2.	OR.	SR.	Cl.	Br.
X·C=C	50	—	400	—	450	50—100	—
X·C=C·C=C	50	150 [1]	650	—	—	60	—
X·C=C·C<O,O	—	—	800	300	—	200	250
X·C=C·C=O	100	—	950	500	850	200	300

[1] Assumed to be the same as in the conjugated vinylacetylene system.

These relationships may be compared with those obtaining when auxochromes are attached to chromophoric systems other than of the open-chain ethylenic type:

(i) In benzene derivatives the largest displacements of the 2000 A. band (regarded as displaced ethylenic absorption) are produced by the amino- and the thiol group, while in all other cases the maximum remains below 2200 A. and has not been recorded (Table II). The low-intensity 2550 A. band (ascribed to the benzenoid

TABLE II.

The Effect of Auxochromes on the Phenyl Chromophore.

(Solvent: *n*-hexane.)

	$\lambda_{max.}$, A.†	$\epsilon_{max.}$	$\lambda_{max.}$, A.†	$\epsilon_{max.}$
Ph·H [1]	1980	8000	2560	250
Ph·CH_3 [2]	*	*	2620	300
Ph·NH_2 [3]	2300	8000	2800	200
Ph·OH [2]	*	*	2750	200
Ph·SH [3]	2350	8500	2690	700
Ph·F [4]	*	*	2670	1650
Ph·Cl [4]	*	*	2650	300
Ph·Br [4]	*	*	2650	250
Ph·I [4]	*	*	2580	800

* Not recorded.

† Values refer to the highest peaks of regions of resolved absorption.

[1] Henri, *J. Phys. Radium*, 1922, **3**, 181. [2] Scheibe, *Ber.*, 1926, **59**, 2617. [3] This paper. [4] Conrad-Billroth, *Z. physikal. Chem.*, 1932, **19**, 76.

chromophore) is displaced by all auxochromic substituents but in a different order from that found in aliphatic systems, namely $CH_3 < NH_2 > OH > F$, OH > SH, F > Cl > Br > I, *i.e.*, $\Delta\lambda_X$ again reaches a maximum with nitrogen in the first period, but decreases on ascending a group of the periodic system.

(ii) In five-membered heterocyclic compounds where the substituent is linked by single bonds to the ends of the conjugated system, the high-intensity absorption near 2000 A., probably representing a displaced band due to the ethylenic group, is but little affected, while the low-intensity absorption near 2400 A., ascribed to the conjugated diene system, is strongly reduced in intensity in pyrrole and furan, and slightly intensified in

thiophen (Table III), $\lambda_{max.}$ remaining almost unchanged. Similarly, in tricyclic dyes formally derived from diphenylmethane or diphenylamine by joining the *o* : *o'*-positions through O, S, or NR groups, the introduction of the latter results, on the average, in hyperchromic effects of −690, −720, and −1570 A. respectively (Lewis, *J. Amer. Chem. Soc.*, 1945, **67**, 770).

TABLE III.

	$\lambda_{max.}$, A.	$\epsilon_{max.}$	$\lambda_{max.}$, A.	$\epsilon_{max.}$
*cyclo*Pentadiene [1]	2000	10,000	2440	2500
Pyrrole [2]	2100	15,000	2400	300
Furan [2]	2000	10,000	2500	1
Thiophen [2]	Not recorded		2350	4500

[1] Scheibe and Grieneisen, *Z. physikal. Chem.*, 1934, *B*, **25**, 52; Henri and Pickett, *J. Chem. Physics*, 1939, **7**, 439 (measurements in vapour phase and hexane solution). [2] Menczel, *Z. physikal. Chem.*, 1927, **125**, 161 (measurements in hexane solution).

(iii) Substituents directly attached to a carbonyl group also produce effects quite different from those observed when they are attached to an ethylenic bond (cf. Herold, *Z. physikal. Chem.*, 1932, **18**, 277; Burawoy, *J.*, 1939, 1177). The carbonyl group itself gives rise to two maxima, one at about 1900 A. (ϵ = *ca.* 10,000) which may be compared to the band near 1800 A. exhibited by olefins and most other compounds containing a multiple linkage, and the other at 2900 A. (ϵ = *ca.* 20) which is peculiar to the carbonyl group (Wolf, *Z. physikal. Chem.*, 1929, *B*, **2**, 35, *et seq*; Mohler, *Helv. Chim. Acta*, 1937, **20**, 285). Only the low-intensity bands have been recorded for compounds of the type R·CO·X, $\lambda_{max.}$ being decreased, most strongly by the amino- and hydroxyl groups, in the order X = NH_2, OH > Cl > CH_3 (Table IV). In α : β-ethylenic carbonyl compounds, a methyl group attached at the carbonyl carbon atom exerts a small bathochromic effect on the band due to the conjugated system; other substituents again have the opposite effect, though in the different order Cl > OH > NR_2.

TABLE IV.

The Effect of Auxochromes on the Carbonyl Chromophore.

X·CH=O (vapour or liquid).

X	H.	CH_3.	NH_2.	OH.	Cl.
$\lambda_{max.}$	295 [1]	290 [2]	*205 [3]	205 [3]	235 [3]
$\epsilon_{max.}$	~10	10	160	45	50

CHMe=CH·CX=O (in alcohol).

X	H.	CH_3.	NEt_2.	OH.	Cl.
$\lambda_{max.}$	217 [4]	224 [5]	215 [6]	204 [7]	<210 [6]
$\epsilon_{max.} \times 10^{-3}$	16	10	11	10	> 8

* Inflexion.

[1] Purvis and McCleland, *J.*, 1912, **101**, 1810. [2] Conrad-Billroth, *Z. physikal. Chem.*, 1933, *B*, **23**, 315. [3] Ley and Arends, *ibid.*, 1931, *B*, **12**, 132. [4] Hausser, Smakula, Kuhn, and Hoffer, *ibid.*, 1935, *B*, **29**, 371. [5] Evans and Gillam, *J.*, 1941, 815. [6] This paper. [7] Mohler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485.

A characteristic property of the ethylenic group and of most other chromophores containing multiple linkages is their ability to transmit conjugation. This chromolatory effect is also shown to varying degrees by auxochromes containing unshared electron pairs. It is well known that in dyes the bathochromic effect of amino-substituents increases in the order NH_2 < NHEt < NEt_2 (cf. Wizinger, " Organische Farbstoffe," Dümmler, Berlin, 1933), *i.e.*, that nitrogen transmits the bathochromic effect of alkyl groups. It has also been shown (Part II, Braude and Jones, *loc. cit.*) that the >NH-group will to a large extent transmit conjugation between two chromophoric systems. Table V shows that this also applies to the −O− and −S− groups, the chromolatory capacity varying in the order N > S > O. No chromolatory effects are displayed, on the

TABLE V.

Chromolatory (Transmitting) Effect of Auxochromes.

(Solvent : Alcohol.)

	$\lambda_{max.}$, A.	$\epsilon_{max.} \times 10^{-3}$.	$\lambda_{max.}$, A.	$\epsilon_{max.} \times 10^{-3}$.	$\Delta\lambda_{Et.}$*
Ph·CO·CH=CH·NH_2	2420	11	3240	19	—
Ph·CO·CH=CH·NHEt	2420	11	3380	23	140
Ph·CO·CH=CH·NEt_2	2420 2450	12	3430	26	95
					$\Delta\lambda_{Ph.}$*
Ph·CO·CH=CH·NH·Ph	2420 2450	18	3740	31	500
Ph·CO·CH=CH·O·Ph	2670 †	15	2820 2910	18 18	(~200)
Ph·CO·CH=CH·S·Ph	2560	14	3350	19	(~300)
Ph·CO·CH=CH·SO_2·Ph	2450	16	2800 †	4	(~0)

* $\Delta\lambda_{Et.}$, $\Delta\lambda_{Ph}$ = displacements of long wave-length band with respect to parent compounds, *e.g.*, Ph·CO·CH=CH·NH_2, Ph·CO·CH=CH·OH, and Ph·CO·CH=CH·SH.

† Inflexion.

other hand, by the methylene and sulphone groups in which the central atom carries no unshared electron pairs. Similar results have been obtained by Chaix (*Bull. Soc. chim.*, 1933, **53**, 700) in an examination of the ultra-violet light absorption of systems Ph·X·Ph, where X = CH_2, NH, O, S, Se, SO, SeO, and SO_2.

Discussion.

Selective absorption in the near ultra-violet region of the spectrum (1800—4000 A.) corresponds to energy increments of between 70 and 160 kg.-cals./mol., intermediate between those required for the photo-ionisation of single covalent bonds and those required for vibrational or rotational transitions. Quanta of this magnitude are involved in the displacement of *mobile electrons* (Lennard-Jones, *Proc. Roy. Soc.*, 1937, *A*, **158**, 280), *i.e.*, electrons *more* mobile than ordinary bonding electrons. The unsaturation electrons of multiple bonds are the most important type of mobile electrons encountered in organic compounds, and it has long been known that the juxtaposition of two or more groups containing multiple bonds gives rise to displacements of the selective absorption towards, and eventually into, the visible region, *i.e.*, to a lowering of the energy requirements of the electronic transitions. These increases in mobility in the classical conjugated systems are paralleled by corresponding changes in other physical properties, *e.g.*, refractivity and heats of formation, and in chemical reactivity, and may be ascribed to enhanced resonance (Bury, *J. Amer. Chem. Soc.*, 1935, **57**, 2115; Pauling, *Proc. Nat. Acad. Sci.*, 1939, **25**, 577).

The bathochromic effects of substituents such as NH_2, OR, and halogens must similarly be attributed to interaction between the unsaturation electrons of the multiple bond and the unshared electron pair of the substituent, resulting in increased resonance and decreased transition energies. Deviations from additivity in physical properties are observed, as well as chemical reactions reminiscent of those found in conjugated systems of two multiple linkages (cf. Bowden, Braude, Jones, and Weedon, *loc. cit.*). These effects disappear if the free electron pair becomes shared; thus the light absorption of compounds XNR_2 (where X is a substituted ethylenic group) reverts to that of XH in strongly acid solutions, and the amine oxide (French and Gens, *J. Amer. Chem. Soc.*, 1937, **59**, 2600) and sulphone groups exert hardly any bathochromic action.

In alkyl and alkylsilico-groups, the central atom carries no unshared electron pair. The small but well-defined bathochromic effects which are nevertheless observed have been related to corresponding variations in the heats of hydrogenation of olefins and discussed under the name of " hyperconjugation " (Price and Tutte, *Proc. Roy. Soc.*, 1940, *A*, **174**, 207; Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41; Mulliken, *Rev. Mod. Physics*, 1942, **14**, 265). The pronounced influence of alkyl substitution on chemical reactivity has been, in part, ascribed to the partial ionic character of the carbon–hydrogen bonds, but the consequent decrease of the effects in the sequence $Me > Et > Pr^{\beta} > Bu^{\gamma}$ has not been realised in the few spectral measurements so far available (Bateman and Koch, *J.*, 1944, 600).

The carbonyl chromophore is affected by substituents in the opposite way to the ethylenic chromophore. This is clearly due to interaction, amply borne out by other physical as well as chemical evidence (Chaplin and Hunter, *J.*, 1937, 1114; Hunter, *J.*, 1945, 806), between the substituents and the carbonyl oxygen, involving a loss in double-bond character of the carbon–oxygen linkage. This interaction may be of two types: direct co-ordination between X^- and $O{=}$, and hydrogen bond formation when X = NHR or OH. Similar effects have been noted in the substituted *p*-benzoquinones (Part I, *J.*, 1945, 490).

There is thus a close parallelism between the variochromic (as well as chromolatory) effects of substituents on ultra-violet light absorption properties and their so-called " tautomeric " effects on chemical reactivity. Both depend on an increase in the contribution of the resonance form $X^+{=}A{-}B^-$ to a hybrid classically represented by $X{-}A{=}B$. Both are dependent on the capacity for covalency increase of X (cf. Ingold, *Chem. Reviews*, 1934, **15**, 225) and are much larger when X is co-ordinatively unsaturated. Both increase with increasing " basicity," *i.e.*, decreasing control of the unshared electron pair by the atomic nucleus, reaching a maximum with nitrogen amongst the non-metals of the first period, and increasing on ascending a group of the periodic system. On this basis a large bathochromic effect may be predicted for tervalent phosphorus in compounds containing the system $-C{=}C{-}P<$, but no examples are at present known.

Experimental.

For details of the light-absorption measurements see Part I (*loc. cit.*).

Most of the compounds employed in this study are described in the preceding paper. Other materials had the following physical constants: Chloroprene (b. p. 59·5°/760 mm.), thiophenol (b. p. 54°/15 mm.; $n_D^{18^\circ}$ 1·5880), methyl β-chlorovinyl ketone (b. p. 72°/100 mm., $n_D^{21^\circ}$ 1·4658), and β-chloroethyl vinyl sulphide (b. p. 45°/15 mm., $n_D^{12^\circ}$ 1·5232). We are indebted to Dr. L. N. Owen for samples of α-methoxycrotonic acid (m. p. 58°), β-methoxycrotonic acid (m. p. 130°), *trans*-α-chlorocrotonic acid (m. p. 99°), and *trans*-α-bromocrotonic acid (m. p. 107°). We are indebted to Dr. S. R. Robinson for the following preparation: 3-*Methyl*-1-*triethylsilicopent*-3-*en*-1-*yne*. Triethylsilicon chloride, prepared from silicon tetrachloride and ethylmagnesium bromide (3·75 mol.), b. p. 142—144°/760 mm. (Found: Cl, 23·4. Calc. for $C_8H_{15}ClSi$: Cl, 23·5%) was treated with the theoretical quantity of the Grignard compound from 1 : 2-dimethylvinylacetylene and ethylmagnesium bromide to give 3-*methyl*-1-*triethylsilicopent*-3-*en*-1-*yne*, b. p. 115—116°/20 mm. (Found: C, 75·1; H, 11·1. $C_{12}H_{22}Si$ requires C, 74·2; H, 11·4%).

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Imperial College of Science and Technology, London, S.W.7 [*Received, April 15th*, 1946.]

208. *Researches on Acetylenic Compounds. Part IX. Heterocyclic Compounds derived from Ethynyl Ketones.*

By Kenneth Bowden and E. R. H. Jones.

With reagents such as hydrazine, hydroxylamine, guanidine, diazomethane, and ammonium carbonate, ethynyl ketones yield the expected heterocyclic products, identical in most cases with those obtained under similar conditions from the hydroxymethylene derivatives of the corresponding methyl ketones.

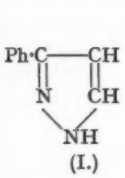
The close similarity between the reactions with amines of ethynyl ketones and hydroxymethylene derivatives, *i.e.*,

$$Ph{\cdot}CO{\cdot}C{\equiv}CH \xrightarrow{PhNH_2} Ph{\cdot}CO{\cdot}CH{=}CH{\cdot}NHPh \xleftarrow{PhNH_2} Ph{\cdot}CO{\cdot}CH{=}CH{\cdot}OH$$

(Bowden, Braude, Jones, and Weedon, this vol., p. 45) suggested that the ethynyl ketones should be converted readily into heterocyclic compounds with appropriate reagents. This has now been found to be so, provided that the reactions are effected under only weakly basic conditions, readily attained by gradually liberating the bases into refluxing aqueous alcoholic solutions of the ketones.

With hydrazine, phenyl ethynyl ketone gives a 70% yield of 3-phenylpyrazole (I), the corresponding 5-phenyl*iso*oxazole being obtained in 90% yield by using hydroxylamine (cf. Claisen, *Ber.*, 1903, **36**, 3665; Moureu and Delange, *Bull. Soc. chim.*, 1904, **31**, 347, 1335; Moureu and Brachin, *ibid.*, p. 343; André, *Ann. Chim.*, 1913, **29**, 590, for similar reactions with substituted acetylenic ketones). Guanidine under similar conditions gives 2-amino-4-phenylpyrimidine (II) in 25% yield, identical with the product obtained by interaction of hydroxymethyleneacetophenone and guanidine nitrate (Benary, *Ber.*, 1930, **63**, 2601).

Hüttel (*Ber.*, 1941, **74**, 1680) has shown that propargyl aldehyde reacts with diazoacetic ester, diazomethane, hydrazoic acid, and phenyl azide, addition taking place exclusively at the acetylenic linkage. Phenyl ethynyl ketone combines with diazomethane at ordinary temperatures giving 3-*benzoylpyrazole* (III) in 85% yield.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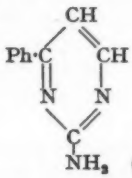
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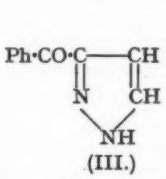
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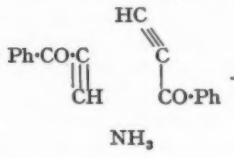

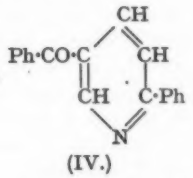
(IV.)

In Part VIII (this vol., p. 945) the simple addition reaction between phenyl ethynyl ketone and liquid ammonia was described. When the ketone is refluxed in alcoholic solution with ammonium carbonate, reaction occurs between two molecules of the ketone and one of ammonia giving 5-benzoyl-2-phenylpyridine (IV) identical with that obtained from the interaction of the sodio-derivative of hydroxymethyleneacetophenone and ammonium acetate (Benary and Psille, *Ber.*, 1924, **57**, 830).

Experimental.

3-Phenylpyrazole (I).—Phenyl ethynyl ketone (6·5 g.) and hydrazine sulphate (6·5 g.) were refluxed with alcohol (75 c.c.) and sufficient water to render the mixture homogeneous. Sodium carbonate (5·3 g.) dissolved in the minimum volume of water was added dropwise to the boiling solution during 1 hour and refluxing was continued for a further 3 hours. After dilution with water and isolation with ether the crude product was purified by sublimation at 50° (bath temp.)/10^{-4} mm. followed by crystallisation from light petroleum (b. p. 40—60°) giving 3-phenylpyrazole (5 g.), m. p. 78°. Both this compound and its picrate showed no depression of m. p. on admixture with authentic specimens obtained by the method of Knorr (*Ber.*, 1895, **28**, 691) from the sodium salt of hydroxymethyleneacetophenone and hydrazine sulphate.

5-Phenylisooxazole.—Phenyl ethynyl ketone (3·25 g.) was dissolved in alcohol (50 c.c.) to which hydroxylamine hydrochloride (1·75 g.) had been added. Whilst refluxing, a small amount of water was added to make the mixture homogeneous. Sodium carbonate (1·3 g.) dissolved in the minimum amount of water was added during 1 hour, and after 9 hours' refluxing the product was isolated with ether. Distillation gave 5-phenyl*iso*oxazole (3 g.), m. p. 23°, b. p. 130°/11 mm. (Claisen and Stock, *Ber.*, 1891, **24**, 135, give m. p. 22—23°). The *iso*oxazole (*ca.* 0·25 g.) was authenticated by warming with methyl alcohol (5 c.c.) to which a small amount of sodium had previously been added. Neutralisation with acetic acid followed by evaporation gave a solid which after crystallisation from water yielded ω-cyanoacetophenone, m. p. 80—81° (Claisen and Stock, *loc. cit.*, give m. p. 80—81°).

2-Amino-4-phenylpyrimidine (II).—Phenyl ethynyl ketone (6·5 g.) was refluxed in alcohol (50 c.c.) with guanidine nitrate (6·1 g.), water being added to give a clear solution, and sodium carbonate (2·65 g.), in the minimum quantity of water, was added whilst refluxing during 2 hours. Refluxing was continued for a further 10 hours and the product was isolated with benzene giving needles of 2-amino-4-phenylpyrimidine (2 g.), m. p. 164°, undepressed on admixture with an authentic specimen obtained from the sodium salt of hydroxymethyleneacetophenone and guanidine nitrate (Benary, *loc. cit.*).

3-Benzoylpyrazole (III).—An ethereal solution of diazomethane, prepared from nitrosomethylurea (5·25 g.), was added dropwise to phenyl ethynyl ketone (3·25 g.) in ether (25 c.c.) at 0—5° until a permanent yellow colour remained. After 12 hours, evaporation of the solution gave a pale yellow solid (3·6 g.) which on sublimation at 65° (bath temp.)/10^{-4} mm. yielded long needles of 3-*benzoylpyrazole*, m. p. 98° (Found: N, 16·4. $C_{10}H_8ON_2$ requires N, 16·4%).

5-Benzoyl-2-phenylpyridine (IV).—Ammonium carbonate (0·72 g.) was dissolved in the minimum quantity of water and phenyl ethynyl ketone (1·3 g.) added in alcohol (15 c.c.). The mixture was refluxed for 2 hours, the solvent removed under reduced pressure, and the product isolated with ether and crystallised from aqueous methyl alcohol followed by

sublimation at 10^{-4} mm. to give 5-benzoyl-2-phenylpyridine (0·75 g.), m. p. 84—85° (Found: N, 5·25. Calc. for $C_{18}H_{13}ON$: N, 5·4%). No depression of m. p. was observed upon admixture with an authentic specimen, m. p. 85° (Benary and Psille, *loc. cit.*). Light absorption in alcohol: Maxima, 2600, 3000A.; ϵ = 8,500 and 28,000 respectively (identical with that of the authentic specimen). The picrate had m. p. 175°, undepressed on admixture with an authentic specimen (Found: N, 11·2. Calc. for $C_{24}H_{16}O_8N_4$: N, 11·45%).

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209. *Unsaturated Lactones. Part I. (Researches on Acetylenic Compounds. Part X.) A New Route to Growth-inhibitory αβ-Ethylenic γ- and δ-Lactones.*

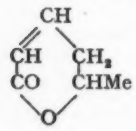
By L. J. HAYNES and E. R. H. JONES.

Certain aspects of the literature concerning growth-inhibitory substances present in animal and plant tissues are briefly reviewed. It seems probable, though not yet established with certainty, that the natural active agents are αβ-unsaturated lactones. The methods employed for the synthesis of such compounds are discussed and a new general procedure for the preparation of αβ-unsaturated γ- and δ-lactones from acetylenic hydroxy-acids is described. A number of lactones synthesised by this route are evaluated according to their inhibitory effects on the germination of cress seeds.

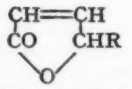
UNSATURATED lactone groupings are frequently encountered as characteristic structural features of many naturally occurring compounds exhibiting diverse types of physiological action. Attention has been drawn to this structural similarity, observed for example in the heart aglycones, fish poisons of the furocoumarin type, antibiotics such as penicillic acid, patulin, etc., by several workers (Houben–Weyl, " Die Methoden der Organischen Chemie," Leipzig, 1930, III, 682; Oxford, *Ann. Rev. Biochem.*, 1945, **14**, 749; Lauger, Martin, and Muller, *Helv. Chim. Acta*, 1944, **27**, 892; Veldstra, *Enzymologia*, 1944, **11**, 373). The scope and siguificance of this correlation have been considerably extended and emphasised by the discovery by Medawar, Robinson, and Robinson (*Nature*, 1943, **151**, 195) that an unsaturated lactone is also effective in controlling the differential growth of animal tissues. Moreover, Kuhn, Jerchel, Moewus, Müller, and Lettré (*Naturwiss.*, 1943, **31**, 468) have observed that a similar lactone, and some related compounds, also exert growth inhibitory effects in the plant kingdom, especially on seed and pollen germination.

Heaton (*J. Path. Bact.*, 1926, **29**, 293; 1929, **32**, 565) demonstrated the presence, in tissue extracts of most adult mammalian organs and also in malt, of a substance which inhibited the growth *in vitro* of explanted chick fibroblasts at concentrations at which the proliferation of epithelial tissues proceeded unchecked. He suggested that the cessation in adults of connective tissue growth, as contrasted with the continued reproduction of epithelial tissue, was to be attributed to the controlling action of this differential growth inhibitor. This work has since been confirmed by Brues, Jackson, and Aub (*Proc. Soc. Exp. Biol. Med.*, 1936, **34**, 270) and by Medawar (*Quart. J. Exp. Physiol.*, 1937, **27**, 147), the last showing that its action extended to all mesenchyme derivatives and that the factor was also present in a variety of ungerminated cereals and in oranges.

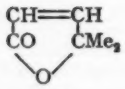
By vigorous steam distillation of a commercial malt extract, Medawar, Robinson, and Robinson (*loc. cit.*) isolated a small quantity of a material, exhibiting the differential growth inhibitory action, for which they suggested the formula $C_6H_8O_2$ and an unsaturated lactone structure. The lactone (I) of pent-1-en-4-ol-1-carboxylic acid (δ-$\Delta^{\alpha\beta}$-hexenolactone) was synthesised in small yield by condensation of acetaldol with malonic acid and was shown to possess growth-inhibitory properties, although to a less marked degree than the product isolated from malt.



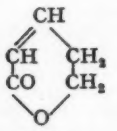
(I.)



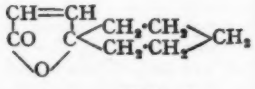
(II; R = Et)
(VI; R = *n*-Pr)
(VII; R = Me)



(III.)



(IV.)



(V.)

A dextrorotatory lactone (the so-called parasorbic acid) to which structure (I) was assigned had been isolated from the berries of the mountain ash (*Sorbus aucuparia*) (Hofmann, *Annalen*, 1859, **110**, 129; Doebner, *Ber.*, 1894, **27**, 344). Kuhn and Jerchel (*Ber.*, 1943, **76**, 413; see also Veldstra, Thesis, Utrecht, 1935) rigidly established the structure of this compound as (I) rather than (II) by hydrogenation to δ-hexolactone, and they synthesised the *dl*-lactone by treatment of 3 : 5-dibromohexoic acid (obtained by the addition of hydrogen bromide to sorbic acid) with hot water. Following the observations of Medawar, Robinson, and Robinson, the action of the *dl*-lactone on the growth of chick fibroblasts *in vitro* was examined (Kuhn, Jerchel, *et al.*, *loc. cit.*) and the synthetic *dl*-compound was found to possess practically the same activity as the natural *d*-parasorbic acid.

The term " blastocholine " was given by Köckemann (*Ber. deut. bot. Ges.*, 1934, **52**, 523) to a material of unknown structure, present in various ripe fruits, which suppressed the germination of cress seeds (*Lepidium sativum*). Blastocholine was found to be both ether and water soluble, insoluble in light petroleum, and stable at 100° in aqueous solution but sensitive to peroxide and alkalis. Köckemann noted the similarity in chemical and physical properties with the auxins, but he showed that blastocholine exhibited no auxin-like activity. Kuhn, Jerchel, *et al.* (*loc. cit.*) showed that both the natural and the synthetic lactone (I) completely inhibit the germination of cress seeds at a concentration of 0·1% and although germination occurs at 0·01% the root lengths are definitely less than those of the controls. With coumarin, at this latter concentration, only 2% of the seeds germinate. It had previously been observed by Cameron (*J. Physical Chem.*, 1910, **14**, 422) that both coumarin and daphnetin prevent the growth of wheat, and Sigmund (*Biochem. Z.*, 1914, **62**, 339) had noted the inhibitory effect of aesculetin and daphnetin on seed germination. Veldstra and Havinga (*Rec. Trav. chim.*, 1943, **62**, 841) have confirmed and extended the results of Kuhn, Jerchel, *et al.*, showing that the isomeric lactone (II) and β-angelicalactone exert similar inhibitory properties, and that 5 : 6- and 7 : 8-benzcoumarins exhibit definite inhibitory effects. It should be noted that the concentrations at which these lactones are effective are very much higher than those required to produce comparable effects with substituted phenoxyacetic acids, etc. (Slade, Templeman, and Sexton, *Nature*, 1945, **155**, 497; Templeman and Sexton, *ibid.*, 1945, **156**, 630).

Certain suggestions have been made as to the possible mode of action of these unsaturated lactones, but it should be emphasised that as yet there is no certainty (as was pointed out by Medawar, Robinson, and Robinson, *loc. cit.*) that hexenolactone (I) is the actual natural growth inhibitor present in either plant extracts [cf. Köckemann, *loc. cit.*; Larsen, *Planta* (*Z. wiss. Biol.*), 1939, **30**, 160] or animal tissues. Medawar *et al.* (*loc. cit.*) suggested the possibility that the growth inhibitory material might interfere with pantothenic acid metabolism,

Light-absorption Data for Unsaturated Lactones.

(in alcoholic solutions)

	λ A.	ε.	Compare:	λ A.	ε.
(I)	2110	10,000			
(III)	2130 *	7,000	$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CH{=}CH{\cdot}CO_2Et$...	2150	10,000
(IV)	2140	8,000	$CH_2OH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CO_2Et$	2130	9,500
(V)	2140	10,000	$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CO_2Et$	2160	6,000
(VI)	2140 *	8,000	$CH_2OH{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CO_2Et$	2130	5,000
(VII)	2140	10,000			

* Maxima, in other cases end absorption only.

but the presence of this acid was found to have no effect on the activity of hexenolactone. Hauschka (*Nature*, 1944, **154**, 769) who employed the flat-worm, *Dugesia tigrina* [which develops a characteristic Y-shaped lesion in M/20,000-hexenolactone (I) solutions], in extensive biological tests, observed that α- and β-alanine and glutathione exerted protective influences at certain concentrations. In later studies (Hauschka, Toennies, and Swain, *Science*, 1945, **101**, 383) the appreciable hexenolactone antagonism found with cysteine led to the postulate that it interfered with thiol metabolism essential to enzyme function. Evidence was produced to show that a direct and reversible interaction occurs between cysteine and the lactone (I) (cf. Geiger and Conn, *J. Amer. Chem. Soc.*, 1945, **67**, 112; Cavallito and Haskell, *ibid.*, p. 1991). Veldstra and Havinga (*loc. cit.*; *Enzymologia*, 1943—1945, **11**, 373) believe that unsaturated lactones function as permeability regulators for protoplasmic membranes, in this way antagonising the action of the plant growth hormones, and they have shown that in the pea test coumarin counteracts the effect of naphthaleneacetic acid.

Two main methods have previously been employed for the synthesis of simple unsaturated lactones. (*a*) Conversion of keto-acids into βγ- or γδ-ethylenic lactones by heating with either acetyl chloride or acetic anhydride (see, *e.g.*, Lukes, *Coll. Czech. Chem. Comm.*, 1929, **1**, 461; Kuhn and Jerchel, *loc. cit.*; Desai, *J.*, 1932, 1079; Qadrat-I-Khuda, *J.*, 1929, 1913; Swain, Todd, and Waring, *J.*, 1944, 548; Wolff, *Annalen*, 1885, **229**, 249; Thiele, Tischbein, and Lossow, *ibid.*, 1901, **319**, 180; Gilmour, *J.*, 1914, **105**, 73; Jacobs and Scott, *J. Biol. Chem.*, 1931, **93**, 139; Cavallito and Haskell, *loc. cit.*). The βγ-unsaturated γ-lactones can generally be isomerised to the more stable αβ-unsaturated compounds by heating with bases, *e.g.*, triethylamine (*e.g.*, Thiele *et al.*, *loc. cit.*; Lukes, *loc. cit.*; Pauly, Gilmour, and Will, *Annalen*, 1914, **403**, 152). (*b*) Simultaneous hydrolysis and dehydrobromination of dibromo-acids, usually on boiling with water or sodium carbonate solution (see, *e.g.*, Lespieau, *Bull. Soc. chim.*, 1905, **33**, 466; Kuhn and Jerchel, *loc. cit.*; Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601; Cavallito and Haskell, *loc. cit.*).

Recently a third method has been extensively exploited for the synthesis of substances containing a β-substituted αβ-unsaturated γ-lactone structure (β-substituted $\Delta^{\alpha\beta}$-butenolides), such as is present in the heart aglycones (Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, **6**, 273). This method consists of the application of the Reformatsky reaction, using bromoacetate, to α-methoxy- or -acetoxy-ketones, the γ-lactones being obtained on hydrolysis (Ruzicka, Reichstein, and Fürst, *Helv. Chim. Acta*, 1941, **24**, 76; Ruzicka, Plattner, and Fürst, *ibid.*, p. 716 and many later papers; Elderfield *et al.*, *J. Org. Chem.*, 1941, **6**, 260, 270, 273, 289; 1942, **7**, 362, 374, 383, 444).

None of these methods is especially convenient for the synthesis of αβ-unsaturated δ-lactones. It has now been found that the semi-hydrogenation of acetylenic hydroxy-acids (Haynes and Jones, this vol., p. 503)

provides a useful route to αβ-unsaturated lactones; syntheses of typical γ- and δ-lactones are illustrated below.

$$Me_2CO + HC{\equiv}CH \longrightarrow Me_2C(OH)\cdot C{\equiv}CH \longrightarrow Me_2C(OH)\cdot C{\equiv}C\cdot CO_2H \longrightarrow \text{(III.)}$$

$$CH_2\cdot CH_2 \;(\text{O}) + HC{\equiv}CH \longrightarrow HO\cdot CH_2\cdot CH_2\cdot C{\equiv}CH \longrightarrow HO\cdot CH_2\cdot CH_2\cdot C{\equiv}C\cdot CO_2H \longrightarrow \text{(IV.)}$$

The partial hydrogenation proceeds readily in methanol solution employing a 5% palladium–barium sulphate catalyst; Raney nickel is insufficiently selective for this purpose. In order to avoid contamination of the product with saturated lactone, it has been found preferable to interrupt the hydrogenation after up to about 90% of the theoretical amount of hydrogen has been absorbed. Distillation of the residue obtained after removal of catalyst and solvent gives the lactones directly in yields of 65—80%, the non-distillable residue consisting of unhydrogenated acid together with polymeric lactone formed by intermolecular dehydration. Although it is convenient to use the crude acetylenic hydroxy-acids obtained by carboxylation of the ethynylcarbinols (Haynes and Jones, *loc. cit.*), care has to be taken to avoid contamination with sulphur compounds, and purification of the "AnalaR" benzene employed in the Grignard reactions by shaking at room temperature with Raney nickel (*e.g.*, Bougault, Cattelain, and Chabrier, *Bull. Soc. chim.*, 1940, **7**, 780) was found to be a useful precaution. In two cases the alternative procedure of semihydrogenating the esters of the acetylenic hydroxy-acids to the corresponding *ethylenic hydroxy-esters*, followed by acidic hydrolysis to the lactones (I and IV), has also been employed. The overall yields, however, are lower than those obtained by the more direct route.

The structure of the C_5 carbinol produced by the reaction of propylene oxide with sodium acetylide in liquid ammonia has been definitely established as pent-1-yn-4-ol, by hydrogenation to methylpropylcarbinol, oxidised subsequently to methyl propyl ketone.

Apart from the limitation imposed on the synthesis of δ-lactones by the availability of oxides, this synthetic method is of general applicability for the γ- and δ-substituted compounds. It has the additional advantage that, by utilising the additive properties of the acetylenic acids, β-amino-, -alkoxyl, -mercapto- and similar substituents can readily be introduced and a range of such γ- and δ-lactones has been made in this manner.

Light-absorption data for the various lactones described in this paper are given in the accompanying Table. It will be noted that, as has been observed by other workers (*inter al.*, Ruzicka, Plattner, and Heusser, *Helv. Chim. Acta*, 1942, **25**, 435; 1944, **27**, 186), αβ-unsaturated lactones exhibit high-intensity absorption at the extreme end of the usual ultra-violet range, maxima only being discernible in certain cases. Similar absorption properties have been found for αβ-ethylenic and αβ-acetylenic esters, but in the latter case the intensities are considerably lower.

These lactones are at present being examined by Dr. Medawar for their selective growth-inhibitory properties on explanted chick fibroblasts. Their effects on the inhibition of the germination of cress seeds are tabulated below.

Effect of Unsaturated Lactones on the Germination of Cress Seeds.

	Concentration, g. per c.c.				
	1 : 2000.	1 : 4000.	1 : 8000.	1 : 16,000.	1 : 32,000.
	Seeds germinated (%).				
(I)	0	0	88	100	96 *
(IV)	0	0	0	80	100 *
(VII)	0	64	96	96	96
(VI)	16	76	92	100	100
(III)	80	100	92	100	100
(V)	32	64	84	100	100

All tests were carried out in 8 cm. Petri dishes, 25 seeds being uniformly distributed on a filter paper moistened with 5 c.c. of solution. The solutions were made up in a 0·3% sodium phosphate buffer solution (pH 7) all tests being controlled by blank determinations using an equal volume of the buffer solution. The percentage of seeds germinated was noted after 72 hours, germination being allowed to proceed at room temperature in the absence of direct sunlight. In all cases, except those marked with an asterisk, the root and stem growth of the germinated seeds was less than in the blank experiments.

Experimental.

Pent-1-yn-4-ol [cf. Kreimeier, U.S.P. 2,106,182 (1938)].—To a solution of sodium acetylide in liquid ammonia (6 l.), prepared from sodium (230 g.) (Heilbron, Jones, and Weedon, *J.*, 1945, 83), propylene oxide (725 g.) which had been freshly distilled through a 24 cm. Dufton column, was added during one hour. The acetylene flow (*ca.* 100 c.c. per minute) was maintained for a further 2 hours and then stopped; the reaction mixture was stirred for 24 hours and then the reaction was interrupted by the gradual addition of ammonium chloride (600 g.) during one hour. After addition of ether (2 l.) the mixture was stirred for a further 30 minutes to complete the decomposition of the sodio-compound. The ammonia was allowed to evaporate overnight and the residual suspension of salt extracted thoroughly with ether. Evaporation of the dried (Na_2SO_4) ethereal solution gave a residue which on distillation in nitrogen gave pent-1-yn-4-ol (305 g.), b. p. 74·6°/100 mm., $n_D^{16°}$ 1·4406 (Found: C, 71·6; H, 9·55. Calc. for C_5H_8O: C, 71·4; H, 9·6%). (Kreimeier, *loc. cit.*, describes methyl-β-ethynylethanol, b. p. 125—130°, $n_D^{25°}$ 1·4225.)

Methyl Propyl Ketone.—A solution of pent-1-yn-4-ol (2 g.) in methyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide (50 mg.) until absorption was complete. (Uptake 1135 c.c. at 16°/765 mm., equivalent to 2·0 F.) Distillation of the residue after removal of catalyst and solvent gave methylpropylcarbinol (1·6 g.) b. p. 118°, $n_D^{20°}$ 1·4052 (Sherrill, Baldwin, and Hass, *J. Amer. Chem. Soc.*, 1929, **51**, 3036, give b. p. 119·5°, $n_D^{20°}$ 1·4060). The α-naphthylurethane separated from light petroleum in spheroids, m. p. 75—76° (Adamson and Kenner, *J.*, 1934, 842, give m. p. 74·5°). Oxidation of the hydrogenation product with chromic acid in acetic acid solution gave methyl propyl ketone, b. p. 102—104°, $n_D^{18·5°}$ 1·3920 (Ceuterick, *Bull. Soc. chim. Belg.*, 1936, **45**, 555, gives b. p. 102—103°, $n_D^{20°}$ 1·39012). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in glistening orange plates, m. p. 143·5—144·5° (Campbell, *Analyst*, 1936, **61**, 393, gives m. p. 143—144°) undepressed on admixture with an authentic specimen.

Lactone of Pent-1-en-4-ol-1-carboxylic Acid (δ-Hexenolactone) (I).—(*a*). A solution of pent-1-yn-4-ol-1-carboxylic acid (42 g.; Haynes and Jones, *loc. cit.*) in methanol (110 c.c.) was shaken with hydrogen in presence of a palladium–barium sulphate catalyst (1·5 g., 5% Pd; Schmidt, *Ber.*, 1919, **52**, 409; Shriner and Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1683) and hydrogenation was interrupted after the absorption of 6·6 l. of hydrogen (theoretical for semihydrogenation, 7·77 l.). The catalyst was filtered off and the solvent evaporated from the filtrate after addition of benzene (50 c.c.). Distillation of the residue gave the lactone of pent-1-en-4-ol-1-carboxylic acid (24·5 g.), b. p. 110°/15 mm., $n_D^{19°}$ 1·4730 (Kuhn and Jerchel, *loc. cit.*, give b. p. 103—105°/14 mm., $n_D^{18°}$ 1·475) (Found : C, 64·45; H, 7·4. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·2%).

(*b*) Ethyl pent-1-yn-4-ol-1-carboxylate (8 g.; Haynes and Jones, *loc. cit.*) in ethyl acetate (25 c.c.) was hydrogenated in the presence of a palladium–barium sulphate catalyst (0·5 g.; 5% Pd) the hydrogenation being interrupted after the absorption of 0·7 l. of gas. Distillation of the residue after removal of catalyst and solvent gave *ethyl pent-1-en-4-ol-1-carboxylate* (5 g.), b. p. 54°/0·02 mm., $n_D^{20°}$ 1·4583 (Found : C, 60·5; H, 9·1. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%). Unchanged acetylenic ester (2·6 g.) was recovered in the higher boiling fraction. The ethylenic hydroxy-ester (3 g.) was refluxed with dilute hydrochloric acid (50 c.c.; 1%) for 1 hour. Isolation by the usual procedure gave the lactone (1·2 g.), b. p. 44°/0·05 mm., $n_D^{20·5°}$ 1·4723.

But-1-yn-4-ol-1-carboxylic Acid.—But-1-yn-4-ol (35 g.; Macallum, U.S.P. 2,125,384; Kreimeier, *loc. cit.*) was carboxylated by the general method described by Haynes and Jones (*loc. cit.*). The Grignard complex separated as a white powder from the benzene solution. *But-1-yn-4-ol-1-carboxylic acid* (18·5 g.; 32·5% conversion) was obtained as a very hygroscopic solid which sublimed at 55° (bath temp.)/10^{-4} mm., m. p. 65° (Found : C, 52·2; H, 5·4. $C_5H_6O_3$ requires C, 52·65; H, 5·3%). Light absorption : $\epsilon = 5000$ at 2130A. The *ethyl* ester, prepared by the general method, had b. p. 90°/0·2 mm., $n_D^{14°}$ 1·4714 (Found : C, 59·0; H, 7·25. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%).

Lactone of But-1-en-4-ol-1-carboxylic Acid (IV).—(*a*) A solution of the above acid (15 g.) in methanol (50 c.c.) was shaken with hydrogen in presence of palladium–barium sulphate catalyst (2 g.; 5% Pd). The hydrogenation was interrupted after 2·90 l. of hydrogen had been absorbed (theoretical for semihydrogenation, 3·21 l.). Removal of catalyst and solvent after the addition of benzene gave the *lactone* (7·9 g.), b. p. 103°/10 mm., $n_D^{17°}$ 1·4827 (Found : C, 59·9; H, 6·3. $C_5H_6O_2$ requires C, 61·2; H, 6·15%).

(*b*) A solution of ethyl but-1-yn-4-ol-1-carboxylate (11 g.) in ethyl acetate (25 c.c.) was hydrogenated in presence of palladium–barium sulphate catalyst (0·5 g.; 5% Pd), the experiment being interrupted after 1·67 l. of gas had been absorbed (theoretical for semihydrogenation, 1·75 l.). Removal of catalyst and solvent gave *ethyl but-1-en-4-ol-1-carboxylate* (9·8 g.), b. p. 120°/14 mm., $n_D^{16°}$ 1·4632 (Found : C, 58·55; H, 8·4. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%). The ethylenic hydroxy-ester (9 g.) was refluxed with N-hydrochloric acid (60 c.c.) for 1 hour. Isolation by the usual procedure gave the lactone (2·8 g.), b. p. 98°/10 mm., $n_D^{19°}$ 1·4807.

Lactone of 2-(1′-*Hydroxy*cyclo*hexyl*)*acrylic Acid* (V).—2-(1′-Hydroxy*cyclo*hexyl)propiolic acid (10 g.; Haynes and Jones, *loc. cit.*) in methanol (50 c.c.) was hydrogenated in the presence of palladium–barium sulphate (0·5 g.; 5% Pd), the experiment being interrupted after 1·35 l. hydrogen had been absorbed (theoretical for semihydrogenation, 1·43 l.). The catalyst was filtered off and the solvent evaporated from the filtrate after the addition of benzene. The residue on distillation gave the lactone (7·6 g.), b. p. 84°/0·1 mm., $n_D^{16°}$ 1·4972 (Found : C, 70·85; H, 7·9. $C_9H_{12}O_2$ requires C, 71·0; H, 7·95%).

Lactone of Hex-1-en-3-ol-1-carboxylic Acid (VI).—Hex-1-yn-3-ol-1-carboxylic acid (32 g.; Haynes and Jones, *loc. cit.*) in methanol (100 c.c.) was hydrogenated in presence of palladium–barium sulphate (2 g.; 5% Pd), the experiment being interrupted after the absorption of 5·39 l. of gas (theoretical, 5·99 l.). Isolation by the usual procedure gave the lactone (23·1 g.), b. p. 73°/0·05 mm., $n_D^{18°}$ 1·4596 (Found : C, 66·35; H, 8·25. $C_7H_{10}O_2$ requires C, 66·65; H, 8·0%).

Lactone of 3-Methylbut-1-en-3-ol-1-carboxylic Acid (III).—3-Methylbut-1-yn-3-ol-1-carboxylic acid (21·3 g.; Haynes and Jones, *loc. cit.*) in methanol (100 c.c.) was hydrogenated in the presence of palladium–barium sulphate (2 g.; 5% Pd) until 3·57 l. of gas had been absorbed (theoretical, 3·97 l.). Isolation by the usual procedure gave the lactone (11·4 g.), b. p. 80°/10 mm., $n_D^{18°}$ 1·4470 (Fittig and Geisler, *Annalen*, 1881, **208**, 49, give b. p. 210°; Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601, give b. p. 127°/72 mm.).

Lactone of But-1-en-3-ol-1-carboxylic Acid (VII).—But-1-yn-3-ol-1-carboxylic acid (10 g.; Haynes and Jones, *loc. cit.*) in methanol (50 c.c.) was hydrogenated in the presence of a palladium–barium sulphate catalyst (0·5 g.; 5% Pd) until 1·8 l. of gas had been absorbed (theoretical, 1·96 l.). Isolation by the usual procedure gave the lactone of but-1-en-3-ol-1-carboxylic acid (β-angelicalactone) (6 g.), b. p. 84°/10 mm., $n_D^{21°}$ 1·4532 (Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601, give b. p. 84·5°/12 mm.).

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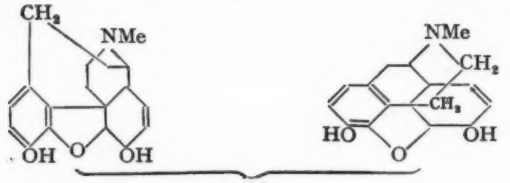
210. *The Synthesis of Analgesic Substances.*

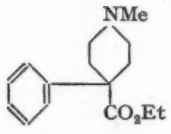
By J. A. Barltrop.

Existing analgesics are briefly reviewed. The preparation is described of α- and β-amino-ketones derived from 5 : 6-dimethoxy- and 5 : 6-methylenedioxy-hydrindone. The introduction of basic side chains into coumarone and *iso*coumaranone and β-tetralone nuclei has been effected by a variety of methods. 5- and 4-(o-*Methoxyphenoxy*)iso*quinoline* have been prepared.

This investigation was undertaken in an attempt to discover synthetic analgesics free from the habit-forming propensities of morphine. Of existing analgesics, the best known, apart from morphine (I) and its derivatives, is pethidine (dolantin, demerol) (II). Many amino-ketones and amino-alcohols derived from partially hydrogenated condensed carbocyclic systems have been tested and found to possess morphine-like activity (cf. Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1933, **55**, 3448; Burger and Mosettig, *ibid.*, 1934, **56**, 1745; 1935, **57**, 2189; Mosettig and May, *J. Org. Chem.*, 1940, **5**, 528). Among heterocyclic systems whose deriv-



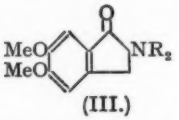
(I.)



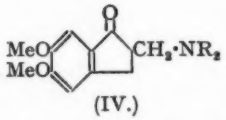
(II.)

atives have been found to be analgesic are coumarone (Bovet, Simon, and Depierre, *Compt. rend. Soc. Biol.*, 1934, **117**, 961), dibenzfuran (Kirkpatrick and Parker, *J. Amer. Chem. Soc.*, 1935, **57**, 1123), benzdioxan (Bovet, *Anesthésie et analgésie*, 1935, **1**, 21), and carbazole (Eddy, *J. Pharm. Exp. Ther.*, 1939, **65**, 294).

In particular, 2-*N*-piperidino-6-methoxy-α-tetralone is claimed to be a morphine substitute. In view of the activity of the latter, and since morphine is a catechol derivative, hydrindones of types (III), (IV), and (V) have been synthesised and tested.



(III.)



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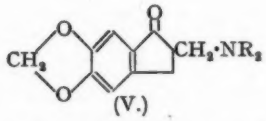
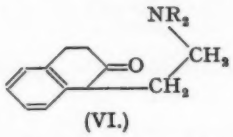


(V.)

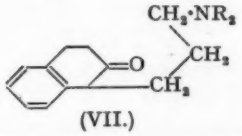
5 : 6-Dimethoxyhydrindone (Perkin and Robinson, *J.*, 1907, **91**, 1081) was brominated and condensed with various secondary amines to give 2-*amino-α-hydrindones* (III, NR_2 = piperidyl, morpholyl, and 1 : 2 : 3 : 4-tetrahydro*iso*quinolyl).

5 : 6-Methylenedioxyhydrindone was prepared from the corresponding phenylpropionic acid (*a*) by cyclisation with phosphoric oxide in benzene (Perkin and Robinson, *J.*, 1907, **91**, 1084), and (*b*) by treatment with phosphorus pentachloride in benzene, followed by stannic chloride. It is noteworthy that Perkin and Robinson (*loc. cit.*), by the action of aluminium chloride on 5 : 6-methylenedioxyphenylpropionyl chloride, obtained the hydrindone in only 15% yield; with stannic chloride a 92% yield was obtained.

By following more or less closely the directions of Harradence and Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938,



(VI.)



(VII.)

72, 284), 5 : 6-methylenedioxy- and 5 : 6-dimethoxy-hydrindone were condensed with paraformaldehyde and various secondary amines to give the Mannich *bases* (IV) and (V). All these compounds were active, the most promising being (III, NR_2 = piperidyl) and (V, NR_2 = 1 : 2 : 3 : 4-tetrahydro*iso*quinolyl).

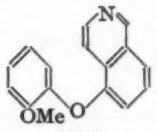
Morphine can be seen to contain a tetralin nucleus alkylated in the 2-position with a dialkylaminoethyl group. In view of the accessibility of β-tetralone obtained by the reduction of 2-methoxynaphthalene (Cornforth, Cornforth, and Robinson, *J.*, 1942, 690), attempts were made to alkylate it with the formation of compounds of types (VI) and (VII).

The above authors have shown (*loc. cit.*) that β-tetralone can be alkylated by means of methyl iodide and sodium *iso*propoxide, but in an attempt to obtain (VI, R = Et) by use of diethylaminoethyl chloride only very small yields were obtained even after prolonged refluxing. Eisleb (*Ber.*, 1941, **74**, 1433), however, has demonstrated that basic side chains of this type may be introduced into compounds containing a reactive methylene group by means of sodamide, and application of this method to β-tetralone resulted in the formation in good yield of the *compounds* (VI, NR_2 = piperidyl, and diethylamino) and (VII, NR_2 = piperidyl).

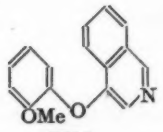
Alternative dissection of the morphine molecule reveals a 5-phenoxy*iso*quinoline skeleton. 5-(o-*Methoxyphenoxy*)iso*quinoline* (VIII) has been synthesised by an Ullmann reaction between guaiacol and 5-iodo*iso*quinoline. The latter was obtained by nitration of *iso*quinoline followed by hydrogenation over Raney nickel catalyst, diazotisation, and treatment with potassium iodide.

Similarly, condensation between guaiacol and 4-bromo*iso*quinoline afforded 4-(o-*methoxyphenoxy*)iso*quinoline* (IX), but owing to the difficulty of obtaining *iso*quinoline under present conditions the series was not further investigated.

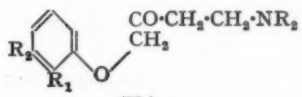
Attention was next turned to coumarones with basic side chains. 2-Methoxy- and 3-methoxy-phenoxyacetone (characterised as 2 : 4-*dinitrophenylhydrazones*) were prepared from the corresponding phenol and



(VIII.)



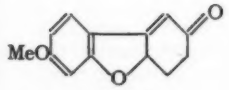
(IX.)



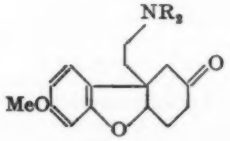
(X.)

chloroacetone in the presence of potassium carbonate (cf. Curd and Robertson, *J.*, 1933, 714), but attempts at preparation of the Mannich bases (X) gave only small yields of products which could not be purified. The ultimate cyclisation to coumarones was not investigated.

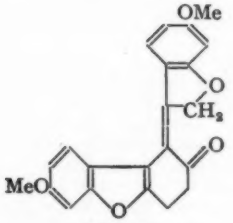
6-Methoxycoumaranone seemed a convenient starting substance for investigations in this series and was prepared by the method of Auwers and Pohl (*Annalen*, 1914, **405**, 265). Stannic chloride, which was found to be effective in the hydrindone series, was used to prepare the substance from 3-methoxyphenoxyacetic acid, but the yields were unsatisfactory. Aluminium chloride was not tried in view of the poor yields obtained by Bridge, Heyes, and Robertson (*J.*, 1937, 285) in the cyclisation of α-(3 : 5-dimethoxyphenoxy)*iso*valeryl chloride to the coumaranone.



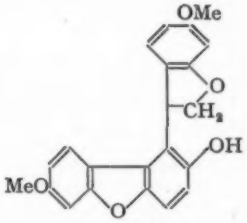
(XI.)



(XII.)



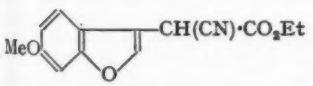
(XIII.)



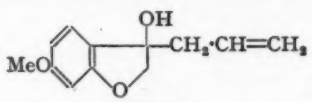
(XIV.)

Attempts were next made to prepare the compound (XII) containing a basic side chain in the angular position occurring in morphine, by Michael addition of ethyl cyanoacetate to the compound (XI) followed by hydrolysis, decarboxylation, reduction, and alkylation. 6-Methoxycoumaranone underwent a Robinson–Mannich reaction with the methiodide of diethylaminobutanone to give an unsaturated *ketone* which, during the subsequent Michael addition, isomerised to a *phenol*. It seems probable that the ketone actually possesses the structure (XIII), being produced by the migration into the furan nucleus of the double bond in the initially formed condensation product (XI), followed by condensation with another molecule of 6-methoxycoumaranone. The isomeric phenol would then be (XIV).

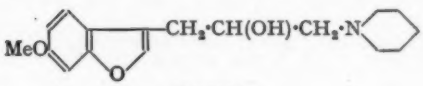
6-Methoxycoumaranone was next condensed with ethyl cyanoacetate according to the directions of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452) with the formation of *ethyl 6-methoxycoumarone-3-α-cyanoacetate* (XV). The yield was poor, and, in view of the more promising trend of subsequent experiments, the projected hydrolysis, decarboxylation, reduction, and alkylation were not carried out. The position of the double bond is not definitely known, but it is considered improbable that it is conjugated with the carbethoxy-group.



(XV.)



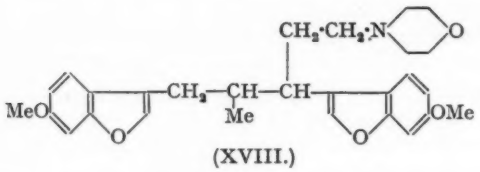
(XVI.)



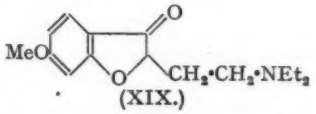
(XVII.)

Reaction of allylmagnesium bromide with 6-methoxycoumaranone produced 3-*hydroxy*-6-*methoxy*-3-*allyl*-*coumaran* (XVI). In this preparation, the order of addition of the reagents was found to be important. The allyl compound was converted into the iodohydrin, and this was treated with piperidine. Piperidine hydriodide was precipitated, indicating the formation of the amino-alcohol (XVII), but this could not be isolated. The free base decomposed on distillation, and attempts at purification through its picrate and picrolonate resulted in hydramine fission and the almost quantitative recovery of piperidine picrolonate. Since a compound as unstable as this would almost certainly be rapidly broken down in the body and thus be inactive, the series was not investigated further.

Addition of hydrogen bromide to the double bond of the hydroxyallylcoumaran by reaction in glacial acetic acid in the presence of benzoyl peroxide gave a bromo-compound, which, when heated with excess morpholine, furnished 6-methoxy-3-morpholinopropylcoumarone, characterised as its *picrate*. When the reaction was repeated on a larger scale the main product was a compound $C_{28}H_{33}O_5N$ (isolated as *hydrochloride*), thought to be (XVIII), containing one morpholine group to two coumarone nuclei.

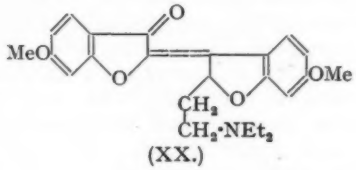


(XVIII.)

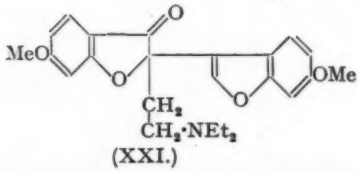


(XIX.)

Alkylation of 6-methoxycoumaranone with diethylaminoethyl chloride in the presence of sodamide afforded, not the desired 6-methoxy-2-β-diethylaminoethylcoumaranone (XIX), but a compound $C_{24}H_{27}O_5N$ (isolated as *hydrochloride*) containing two coumarone nuclei to one basic side chain, whose probable structure is either (XX)

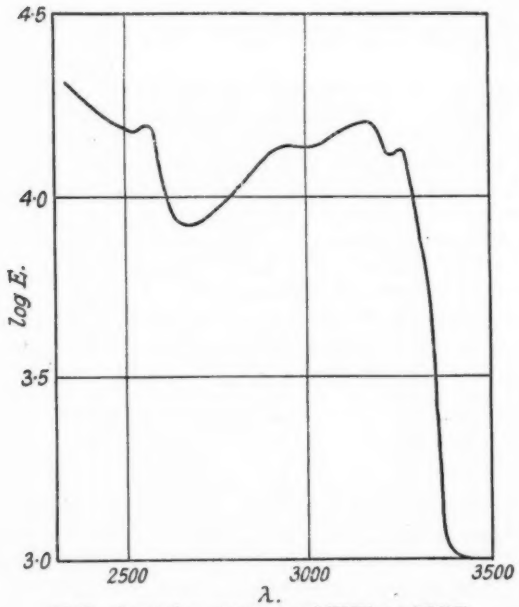


(XX.)



(XXI.)

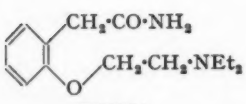
or (XXI). The ultra-violet absorption spectrum of the substance, while not affording conclusive evidence, points to (XX) as the more probable.



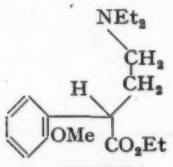
U.V. absorption spectrum of (XX) *or* (XXI).

Attention was next turned to *iso*coumaranones, which, it was thought, might be alkylated in the 3-position with dialkylaminoalkyl halides. The compounds so produced would be especially interesting in that the molecule would contain the reactive groups of pethidine (II) in the same relative position, and in addition, would be stabilised by ring formation.

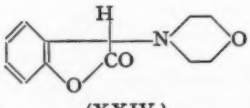
2-Hydroxy-3-methoxyphenylacetic acid was prepared from 2-*hydroxy*-3-*methoxybenzylidene azlactone*. It is noteworthy that the hydroxyl group is so sterically hindered that acetylation did not take place in the azlactone formation. Attempts at cyclisation of the phenylacetic acid were unsuccessful. Even the most drastic conditions failed to produce an appreciable yield of the *iso*coumaranone—another instance of the steric hindrance associated with this hydroxyl group. At this point it was decided to carry out model experiments on *iso*coumaranone itself. Alkylation of this compound with diethylaminoethyl chloride and sodamide gave, not the desired 3-diethylaminoethyl*iso*coumaranone, but 2-β-*diethylaminoethoxyphenylacetamide* (XXII) by opening of the ring followed by alkylation of the resulting sodium aryloxide.



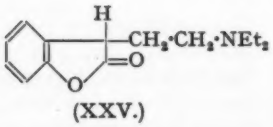
(XXII.)



(XXIII.)



(XXIV.)



(XXV.)

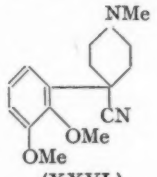
The *hydrobromide* of 3-*morpholino*iso*coumaranone* (XXIV) was obtained by interaction of morpholine and 3-bromo*iso*coumaranone.

2-Methoxybenzaldehyde was hydrogenated with Woodward's (*J. Amer. Chem. Soc.*, 1940, **62**, 1480) activated platinum oxide catalyst to the benzyl alcohol, which was converted into 2-methoxybenzyl cyanide *via* the bromide. This was alkylated in good yield with diethylaminoethyl chloride and sodamide with the formation

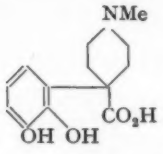
of 2-methoxy-α-(β-diethylaminoethyl)benzyl cyanide, characterised as its *oxalate*. Hydrolysis of the cyanide followed by esterification gave *ethyl 2-methoxy-α-(β-diethylaminoethyl)phenylacetate* (XXIII).

Simultaneous demethylation and hydrolysis of the alkylated cyanide furnished a syrupy amino-acid hydrobromide which on distillation with fused sodium acetate was converted into 3-β-diethylaminoethyl*iso*coumaranone (XXV), characterised as its *picrate*.

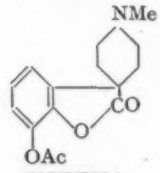
2 : 3-Dimethoxybenzaldehyde was condensed with rhodanine (cf. Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1127), and the resulting 2 : 3-*dimethoxybenzylidenerhodanine* was hydrolysed to 2 : 3-*dimethoxyphenylthiopyruvic acid*. This on oximation and dehydration with acetic anhydride furnished 2 : 3-dimethoxybenzyl



(XXVI.)



(XXVII.)



(XXVIII.)

cyanide, which was also obtained from the aldehyde *via* the alcohol (crossed Cannizzaro reaction) and bromide. Alkylation of the cyanide with methyl-2 : 2′-dichlorodiethylamine and sodamide gave 4-cyano-4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine (XXVI), which has since been described by Bergel, Haworth, Morrison, and Rinderknecht (*J.*, 1944, 262). Simultaneous hydrolysis and demethylation of the cyanide afforded the *hydrobromide* of *4-carboxy-4-(2′ : 3′-dihydroxyphenyl)-1-methylpiperidine* (XXVII). This acid was cyclised with acetic anhydride with the production of the *spiro*piperidino*iso*coumaranone (XXVIII) (characterised as *oxalate* and *picrate*), which not only contains a system occurring in the morphine molecule but is also a ring-closed modification of the pethidine molecule.

Experimental.

2-Bromo-5 : 6-dimethoxyhydrindone (cf. Perkin, Rây, and Robinson, *J.*, 1926, 948).—Bromine (5 g.), dissolved in chloroform (5 c.c.), was slowly added with stirring and ice-cooling to a solution of the dimethoxyhydrindone * (5 g.) in chloroform (10 c.c.). After being stirred for 30 mins. at 0°, the paste was kept at room temperature for 30 mins. and then cooled to 0°. The bromo-ketone was precipitated with ligroin, collected, washed with ligroin, and extracted (Soxhlet) with ligroin (b. p. 40—60°); it was obtained as a pale yellow powder (6·9 g.), m. p. 157°.

Condensation of Bromodimethoxyhydrindone with Secondary Amines.—The bromohydrindone (2 g.), dissolved in acetone (40 c.c.), was added to a solution of the secondary amine (2·1 mols.) in acetone (5 c.c.). After several hours, addition of ether (200 c.c.) precipitated the secondary amine hydrobromide, which was collected. The amino-ketone hydrochloride was obtained by passing hydrogen chloride over the surface of the filtrate, collection, and crystallisation. *2-N-Piperidino-5 : 6-dimethoxyhydrindone hydrochloride* (1·95 g.) crystallised from ethanol–ethyl acetate in colourless needles, m. p. 236° (Found : C, 61·2; H, 7·0; N, 3·9. $C_{16}H_{21}O_3N$,HCl requires C, 61·6; H, 7·1; N, 4·5%). *2-N-Morpholino-5 : 6-dimethoxyhydrindone hydrochloride* (1·5 g.) crystallised from ethanol in colourless needles, m. p. 212° (vac.) (Found : C, 56·7; H, 6·3; N, 4·9. $C_{15}H_{19}O_4N$,HCl requires C, 57·4; H, 6·4; N, 4·5%). *2-N-(1′ : 2′ : 3′ : 4′-Tetrahydroisoquinolino)-5 : 6-dimethoxyhydrindone hydrochloride* (2 g.) crystallised from ethanol in colourless needles, m. p. 188° (Found : C, 63·9; H, 6·2; OMe, 16·5; Cl, 9·4. $C_{20}H_{21}O_3N$,HCl,H_2O requires C, 63·6; H, 6·4; OMe, 16·4; Cl, 9·4%).

2-Morpholinomethyl-5 : 6-dimethoxyhydrindone (Harradence and Lions, *loc. cit.*).—The hydrochloride crystallised from aqueous ethanol in radiating clusters of fine yellow needles, m. p. 183° (yield, 35%).

5 : 6-Methylenedioxyhydrindone.—To a solution in benzene (20 c.c.) of 3 : 4-methylenedioxyphenylpropionic acid (3·9 g.) (prepared in almost quantitative yield by hydrogenating the corresponding cinnamic acid over Raney nickel in dioxan solution at 80°) was added phosphorus pentachloride (5 g.), and the whole was kept at room temperature for 2 hours and then cooled in ice. Stannic chloride (5 g.), dissolved in benzene (8 c.c.), was added, and the mixture shaken for 10 minutes, during which time a yellow solid was gradually deposited. After the mixture had been poured on ice and concentrated hydrochloric acid (30 c.c.) and extracted several times with ether, the combined extracts were washed successively with 10% hydrochloric acid (3 times), water, 10% sodium hydroxide solution (twice) and water, and dried. On evaporating the solvents, colourless crystals of the hydrindone (3·2 g., 92%) remained and were purified by extraction (Soxhlet) with ether. It crystallised in colourless plates, m. p. 161—162° alone or mixed with an authentic specimen.

Preparation of Mannich Bases from 5 : 6-Methylenedioxyhydrindone.—The hydrindone (3 g.), paraformaldehyde (0·9 g., 1·76 mols.), secondary amine hydrochloride (1 mol.), and ethanol (15 c.c.) were refluxed on the steam-bath for the times given below. The Mannich base hydrochloride was gradually deposited, and after cooling was collected and crystallised.

2-N-Morpholinomethyl-5 : 6-methylenedioxyhydrindone. Refluxed for 1 hour. The *hydrochloride* (4·0 g.) crystallised from aqueous ethanol in glistening, rectangular plates, m. p. 183° (vac.) (Found : C, 57·3; H, 6·0; N, 4·9. $C_{15}H_{17}O_4N$,HCl requires C, 57·5; H, 5·75; N, 4·5%).

2-N-Piperidinomethyl-5 : 6-methylenedioxyhydrindone. Refluxed for 4 hours. The *hydrochloride* (2·6 g.) crystallised from ethanol–ethyl acetate in colourless needles, m. p. 172—173° (vac.) (Found : C, 62·1; H, 6·5; N, 4·55. $C_{16}H_{19}O_3N$,HCl requires C, 62·0; H, 6·45; N, 4·5%).

2-N-(1′ : 2′ : 3′ : 4′-Tetrahydroisoquinolinomethyl)-5 : 6-methylenedioxyhydrindone. Refluxed for 30 minutes in ethanol (10 c.c.). The *hydrochloride* after several crystallisations from aqueous ethanol formed colourless needles (1·2 g.), m. p. 172° (vac.) (Found : C, 66·85; H, 5·7; N, 4·2. $C_{20}H_{19}O_3N$,HCl requires C, 67·1; H, 5·6; N, 3·9%).

2-Keto-1-(β-diethylaminoethyl)-1 : 2 : 3 : 4-tetrahydronaphthalene.—(A) Sodium (0·845 g.) was dissolved in dry *iso*propyl alcohol (20 c.c.). Air was displaced from the apparatus by nitrogen, and β-tetralone (6·05 g.), dissolved in dry *iso*propyl alcohol (10 c.c.), was added, followed by diethylaminoethyl chloride (5·8 g.). After being heated on the steam-bath for

* Sir Robert Robinson has drawn the author's attention to the fact that the m. p. of 5 : 6-dimethoxyhydrindone is incorrectly given (Perkin and Robinson, *J.*, 1907, **91**, 1084) owing to a clerical error. This has been examined and it is found that the substance, crystallised from ethanol, has m. p. 120°.

28 hours, during which time a little sodium chloride was deposited, the mixture was diluted with water and acidified with hydrochloric acid out of contact with air. The solvent was removed under reduced pressure and the unchanged β-tetralone extracted with ether. The aqueous layer was basified, and the liberated amine isolated with ether and distilled in bulbs. The diethylaminoethyltetralone (30 mg.), a colourless oil, was collected at 100—140°/0·1 mm. It gave an oily picrate. The oxalate had m. p. 146° undepressed by the oxalate described in (B).

(B) β-Tetralone (5·0 g.) and diethylaminoethyl chloride (4·6 g.) were dissolved in toluene (25 c.c.). Air was displaced from the apparatus with nitrogen, and finely powdered sodamide (1·4 g.) added gradually with agitation. The temperature was kept below 35° during the addition, and then slowly raised to 85° and maintained there for 5 hours, stirring being continued. The mixture was finally boiled under reflux for 1 hour and extracted with hydrochloric acid. The aqueous extract was washed several times with ether, basified, and the liberated base isolated with ether and fractionated in a vacuum. The amino-ketone (6·0 g.), a colourless liquid with a pale blue fluorescence, was collected at 128°/0·08 mm. The compound gives a green coloration with concentrated sulphuric acid and darkens on keeping. The *oxalate* crystallised from ethanol in fine, colourless needles, m. p. 146° (Found : C, 64·6; H, 7·6; N, 4·15. $C_{15}H_{23}ON,C_2H_2O_4$ requires C, 64·5; H, 7·4; N, 4·2%). Raising the temperature more rapidly in this and the other alkylations described below reduces the yield.

2-*Keto*-1-(β-*piperidinoethyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—β-Tetralone (4·9 g.) and piperidinoethyl chloride (5·0 g.), dissolved in toluene (50 c.c.), were treated with sodamide (1·55 g.) as in the preceding experiment, with cooling. When heat evolution had ceased, the mixture was heated to 40° for 1 hour, then 75° for 1 hour, 85° for 1 hour, 100° for 1½ hours and finally refluxed for 1½ hours. The product was worked up as in the preceding experiment. The *piperidinoethyltetralone* (4·8 g.), a viscous pale yellow oil, was collected at 148—152°/0·06 mm. (Found : C, 78·9; H, 8·8. $C_{17}H_{23}ON$ requires C, 79·4; H, 8·95%). The product boils with decomposition.

2-*Keto*-1-(γ-*piperidinopropyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Sodamide (1·6 g.) was added with agitation as in experiment (B) above to a mixture of β-tetralone (5·0 g.), piperidinopropyl chloride (6·1 g.) (Hromatka, *Ber.*, 1942, **75**, 131), and toluene (50 c.c.). After 2 hours' heating at 100°, piperidinopropyl chloride (3 g.) was added, and the mixture boiled under reflux for 2 hours. The product was isolated as in the preceding experiments. The *piperidinopropyltetralone* (4·0 g.), a very viscous, pale yellow oil, was collected at 170°/0·18 mm. (Found : C, 79·3; H, 9·2; N, 5·1. $C_{18}H_{25}ON$ requires C, 79·7; H, 9·2; N, 5·2%). The oxalate, hydrochloride, picrate, and picrolonate were oily.

5-*Amino*iso*quinoline*.—5-Nitroisoquinoline (10 g.) (Claus and Hofmann, *J. pr. Chem.*, 1893, **47**, 252), dissolved in ethanol, was hydrogenated over Raney nickel for 6 hours at 80° with initial pressure 130 atmospheres. The product was isolated in the usual manner and distilled. 5-Aminoisoquinoline (7·5 g., 95%) was collected at 196°/18 mm

5-(o-*Methoxyphenoxy*)iso*quinoline*.—5-Iodoisoquinoline [prepared from 5-aminoisoquinoline (Edinger, *J. pr. Chem.*, 1896, **53**, 379)] (4·3 g.), potassium hydroxide (3·8 g.), guaiacol (8·6 g.), and a trace of copper powder were heated for 4 hours in an oil-bath at 230°. After the aqueous layer had been acidified, extracted with ether, and basified, the liberated oil was isolated with ether and distilled in bulbs. The phenoxyisoquinoline (0·65 g.), a colourless oil, was collected at 90° (bath temp.)/0·15 mm. The *picrate* crystallised from ethanol in yellow needles, m. p. 206° (Found : C, 54·7; H, 3·2. $C_{16}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 55·0; H, 3·3%).

4-(o-*Methoxyphenoxy*)iso*quinoline*.—4-Bromoisoquinoline (7·6 g.) (prepared by rearranging the perbromide), guaiacol (5·7 g.), potassium hydroxide (2·05 g.), and activated copper powder (0·1 g.) were heated in an oil-bath at 190° till the reaction started and then at 210—230° for 2 hours. The product was taken up in dilute hydrochloric acid, washed with ether, and basified, and the liberated amines were isolated with ether and distilled in bulbs. The phenoxyisoquinoline, a colourless oil (2·7 g.), was collected at 130—140° (bath temp.)/0·06 mm. The *picrate* crystallised from much ethanol in fine, yellow needles, m. p. 223° (Found : C, 54·8; H, 3·3; N, 11·65. $C_{16}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 55·0; H, 3·3; N, 11·7%).

3-*Methoxyphenoxyacetone*.—3-Methoxyphenol (43 g.), chloroacetone (47 g.), potassium carbonate (86 g.), and acetone (160 c.c.) were refluxed on the steam-bath for 2 hours. Most of the acetone was removed, excess of sodium hydroxide solution added, and the ketone isolated with ether. The brown oil so obtained was fractionated in a vacuum, the phenoxyacetone (27 g.), a yellow oil, being collected at 138—149°/11 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in fine orange needles, m. p. 140·5—141·5° (Found : C, 53·2; H, 4·7; N, 15·35. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·4; N, 15·55%).

2-*Methoxyphenoxyacetone*.—Guaiacol (10 g.), chloroacetone (11 g.), potassium carbonate (20 g.), and acetone (40 c.c.) were refluxed on the steam-bath for 2 hours. The product was isolated as in the preceding experiment. The fraction, b. p. 135—138°/11 mm. (9·3 g.), was collected and refractionated. The phenoxyacetone (9·0 g.), a yellow oil, was collected at 138°/11 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in spherical clusters of fine, orange needles, m. p. 141·5° (Found : C, 53·3; H, 4·4; N, 15·8. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·4; N, 15·55%).

Attempted Preparation of 1-N-*Morpholino*-3-*keto*-4-(o-*methoxyphenoxy*)*butane*.—2-Methoxyphenoxyacetone (4·63 g.), paraformaldehyde (1·0 g.), morpholine hydrochloride (3·09 g.), and ethanol (15 c.c.) were refluxed on the steam-bath for 6 hours. Water (20 c.c.) was added and the ethanol removed under reduced pressure. The aqueous layer was extracted several times with ether to remove unchanged ketone, filtered, and evaporated under reduced pressure to give the crude hydrochloride as an orange syrup which could not be crystallised. It was converted into the free base, which was freed from morpholine by washing with water, and thence into the picrate, picrolonate, and oxalate. These were also intractable oils. Attempts at distillation of the free base in high vacuum caused complete decomposition.

Attempted Preparation of 1-N-*Morpholino*-3-*keto*-4-(m-*methoxyphenoxy*)*butane*.—3-Methoxyphenoxyacetone (12 g.), paraformaldehyde (1·5 g.), morpholine hydrochloride (6·1 g.), and ethanol (45 c.c.) were refluxed on the steam-bath for 7 hours. The product was worked up as in the preceding experiment. From the ether extracts unchanged phenoxyketone (9·2 g.) was recovered. The free base gave no crystalline derivatives, and distillation in high vacuum caused extensive decomposition; the few drops of distillate obtained gave an oily hydrochloride and picrate.

6-*Methoxycoumaranone*.—(A) The coumaranone was obtained in 84·5% yield from 2-hydroxy-4-methoxychloroacetophenone (see Auwers and Pohl, *Annalen*, 1914, **405**, 265).

(B) Phosphorus pentachloride (6·9 g.) was added to *m*-methoxyphenoxyacetic acid (Koelsch, *J. Amer. Chem. Soc.*, 1931, **53**, 304) (5 g.) suspended in dry benzene (50 c.c.). After being kept for 1 hour and finally warmed gently, the solution was cooled in ice and treated with a cold solution of stannic chloride (3·7 c.c.) in benzene (10 c.c.). A cerise-coloured precipitate gradually formed. After 1 hour at room temperature, the mixture was poured on ice and extracted with ether. The extract was washed with water, sodium carbonate solution, and again with water, and finally dried and evaporated. The residual pink solid (0·95 g.) when crystallised twice from ethanol formed yellow needles, m. p. 119° alone and when mixed with an authentic specimen of 6-methoxycoumaranone.

Condensation of 6-*Methoxycoumaranone with* 1-*Diethylamino*-3-*ketobutane Methiodide*.—6-Methoxycoumaranone (6·6 g.) and sodamide (1·56 g.) were stirred in dry ether (30 c.c.) for 4 hours at room temperature in a stream of nitrogen. The mixture darkened. The methiodide of diethylaminobutanone, prepared from amine (9·6 g.) and methyl iodide (11·4 g.), was dissolved in dry ethanol and added slowly. Agitation was continued at room temperature for 3 hours, and the mixture was then kept overnight and boiled under reflux for 1½ hours. Hydrochloric acid and ether were added

and the product, a black tarry syrup, was isolated with ether. It was dissolved in ethanol and filtered, and the ethanol evaporated. The dark oil was distilled in bulbs. An orange resin (1·8 g.) collected at 200—260° (bath temp.)/0·4 mm., and crystallised on scratching with warm ethanol. The *product* crystallised from ethanol in pale yellow needles, m. p. 184—185° (Found: C, 72·9; H, 5·0. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%). It immediately decolorised potassium permanganate solution and gave a 2 : 4-dinitrophenylhydrazone.

Isomerisation of the above Robinson–Mannich Condensation Product.—The above unsaturated ketone (0·22 g.), ethyl cyanoacetate (0·116 g.), and 0·46 c.c. of a solution of sodium (0·75 g.) in dry ethanol (15 c.c.) were heated on the steam-bath for 6 hours, kept overnight, and refluxed for a further 3 hours. The reaction mixture was diluted with water (20 c.c.) containing acetic acid (0·9 g.) and extracted twice with ether, and the extracts were dried and evaporated. The *compound* (0·15 g.) crystallised from ethanol in long, lemon-yellow needles, m. p. 184—185°, depressed by the Robinson–Mannich condensation product (Found: C, 72·7; H, 5·0; *M*, 335. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%; *M*, 362). The product was sparingly soluble in sodium hydroxide, and gave a brown coloration with ferric chloride. It did not form a 2 : 4-dinitrophenylhydrazone and did not decolorise potassium permanganate.

Ethyl 6-Methoxycoumarone-3-α-cyanoacetate.—6-Methoxycoumaranone (10 g.), ethyl cyanoacetate (7·1 g.), ammonium acetate (1 g.), acetic acid (3 g.), and benzene (15 c.c.) were heated in an oil-bath at 130—150° in a flask fitted with a continuous water separator. Heating was continued for 9 hours. After being cooled and washed with water, the benzene layer was dried and evaporated, and the black residual oil crystallised by trituration with ethanol–ligroin. The solid (7·2 g.), m. p. 112—119°, was collected and distilled in bulbs. The main fraction (6·0 g.) was collected at 120° (bath temp.)/0·03 mm. as a colourless solid, m. p. 119—120° alone and when mixed with an authentic specimen of 6-methoxycoumaranone. The other fraction (0·4 g.), an orange sublimate, was collected at 130—150° (bath temp.)/0·03 mm. The *coumarone-cyanoacetate* crystallised from ethanol in pale orange needles, m. p. 174—175° (Found: C, 64·9; H, 5·15; N, 5·1. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%); it gave a deep rose colour with concentrated sulphuric acid, becoming yellow on warming.

3-Hydroxy-6-methoxy-3-allylcoumaran.—Powdered magnesium–aluminium alloy (60 g. containing 7% of Al) was covered with dry ether (160 c.c.), a crystal of iodine added, and a solution of allyl bromide (41 c.c.) in ether (200 c.c.) run in during 4 hours with stirring. Agitation was continued for a further 4 hours, and the mixture kept overnight. The ethereal solution of the Grignard reagent was filtered through glass wool and added slowly with stirring to a solution of 6-methoxycoumaranone (18 g.) in ether (700 c.c.). Next day, ice was added and then dilute acetic acid until all the solid dissolved. The ethereal layer was separated, washed with water, dried, and evaporated, and the residual oil fractionated. The *coumaran* (15·2 g., 67%), a pale yellow oil, was collected at 154°/18 mm. (Found: C, 69·6; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It decolorised potassium permanganate solution and gave red colorations with alcoholic picric acid and 1 : 3 : 5-trinitrobenzene.

Increasing the proportion of coumaranone to Grignard reagent diminished the yield somewhat, and reversed addition of the coumaranone to the Grignard reagent gave very little of the condensation product, much coumaranone being recovered.

Attempted Preparation of 6-Methoxy-3-(γ-piperidino-β-hydroxypropyl)coumarone.—(A) The above coumaran (2·06 g.) was shaken in ethanol-free ether with yellow mercuric oxide (1·3 g.) and water (0·2 c.c.). Iodine (2·54 g.) was added in portions during 1 hour and shaking continued for a further 2 hours. The solution was filtered, washed with potassium iodide solution, sodium bisulphite solution, and water, and then dried, and the ether evaporated under reduced pressure. The crude iodohydrin remained as an oil which could not be distilled. To this was added piperidine (3 g.) dissolved in ether (6 c.c.); fine colourless needles of piperidine hydriodide (m. p. 172°) were deposited after standing at room temperature for 16 hours and dilution with ether, the solution was extracted several times with water to remove piperidine and its hydriodide, and the ether evaporated under reduced pressure. The crude base was converted into the picrate, an oil which eventually solidified. Attempts at purification by crystallisation from ethanol caused progressive darkening and decomposition, and only piperidine picrate was isolated.

(B) The coumaran (8·24 g.) was converted into the iodohydrin, and treated with piperidine (6·8 g.). After some time, excess of dry ether was added to precipitate all the hydriodide, which was removed. The condensation product was worked up as above, and kept over concentrated sulphuric acid in a vacuum desiccator until no more piperidine was lost. The residual viscous oil (1·3 g.) was converted into its picrolonate in acetone and crystallised from acetone. Piperidine picrolonate (1·1 g.), m. p. 248° undepressed by authentic salt, was isolated, and also 70 mg. of a picrolonate, m. p. >280°. This on recrystallisation darkened and gave more piperidine picrolonate.

6-Methoxy-3-morpholinopropylcoumarone.—The coumaran (0·94 g.) was added dropwise to 1·4 g. of an ice-cold solution prepared from hydrogen bromide (63 g.) and acetic acid (142 g.), with addition of benzoyl peroxide (0·1 g.). After 24 hours at 0°, the viscous, deep red solution was taken up in chloroform, washed with sodium carbonate solution and with water, then dried and evaporated under reduced pressure. The red, residual oil (1·4 g.) was refluxed with morpholine (2·3 g.) in ethanol (20 c.c.) for 14 hours. The ethanol was distilled, water added, and the base extracted with ether. The ethereal solution was washed several times with water and then extracted with dilute hydrochloric acid. The acid layer was basified, and the amine isolated with ether and converted into the *picrate* (0·2 g.), which crystallised from ethanol in yellow rods, m. p. 177—178° (darkening) (Found: C, 52·3; H, 5·0; N, 11·4. $C_{16}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 52·4; H, 4·8; N, 11·1%).

(B) The coumarane (15 g.) was converted into the bromide and boiled under reflux with morpholine (35 g.) for 3 hours, and the product taken up in ether. The ethereal solution was washed repeatedly with water until the washings were no longer alkaline, and then extracted several times with 10% hydrochloric acid. The aqueous layer deposited a brown oil (*a*) (6 g.), which gradually solidified and was collected. The filtrate was basified and the amine (*b*) (2 g.) isolated with ether.

The substance (*a*) was obtained as its *hydrochloride* in colourless needles, m. p. 270°, by extraction (Soxhlet) with ethyl acetate and crystallisation from ethanol (Found: C, 66·9; H, 7·05; N, 2·9; OMe, 11·4. $C_{28}H_{33}O_5N,HCl$ requires C, 67·3; H, 6·8; N, 2·8; OMe, 12·4%). The amine (*b*) gave an oily picrate from which was isolated a small quantity of the picrate of morpholinopropylcoumarone, m. p. 177—179°.

Alkylation of 6-Methoxycoumaranone with Diethylaminoethyl Chloride.—The finely powdered coumaranone (4·9 g.), diethylaminoethyl chloride (4·4 g.), and toluene (50 c.c.) were stirred, and pulverised sodamide (1·4 g.) was added in portions, the temperature being kept below 35°. When all the sodamide had been added, the temperature was raised gradually to 90° and maintained there for 8 hours, during which time the mixture darkened considerably. The reaction was completed by boiling under reflux for 2 hours. The mixture was washed with water and extracted with 18% hydrochloric acid. The acid extract rapidly deposited crystals of the *hydrochloride*, which crystallised from ethanol in pale yellow needles (5 g.), m. p. 233° (Found: C, 64·4, 64·3; H, 6·3, 6·4; N, 3·4, 2·8; OMe, 13·0. $C_{24}H_{27}O_5N,HCl$ requires C, 64·6; H, 6·3; N, 3·15; OMe, 13·9%).

2-Hydroxy-3-methoxybenzylidene Azlactone.—*o*-Vanillin (100 g.), hippuric acid (140 g.), fused sodium acetate (50 g.), and acetic anhydride (250 c.c.) were heated on the steam-bath for 2 hours. After cooling, the *azlactone* was collected as a salmon-pink solid, which was washed with water; it crystallised from glacial acetic acid in thin, orange plates (132 g.),

m. p. 202°. The analytical specimen when recrystallised was pale yellow and had m. p. 203° (Found: C, 69·1; H, 4·4; N, 5·1. $C_{17}H_{13}O_4N$ requires C, 69·2; H, 4·4; N, 4·75%).

2-Hydroxy-3-methoxyphenylacetic Acid.—The above azlactone (114 g.) was dissolved in 10% sodium hydroxide solution (1140 c.c.). Air was displaced from the apparatus by nitrogen, and the mixture was boiled under reflux in an atmosphere of nitrogen for 5 hours and then cooled in ice. 6% Hydrogen peroxide (600 c.c.) was added to half the resulting mixture with agitation. The temperature slowly rose. The next day, the solution was acidified with hydrochloric acid and steam-distilled to remove benzoic acid, much tar being formed during the process. The phenylacetic acid was isolated with ether and distilled. The acid (11 g.) was collected at 150—158°/28 mm. as a pale yellow solid, m. p. 124°. Much residue remained in the flask.

Attempted Cyclisation of 2-Hydroxy-3-methoxyphenylacetic Acid.—(A) The acid was heated in a metal-bath at 250° for 2 hours and then distilled under reduced pressure. The acid was recovered almost quantitatively. (B) The acid was distilled under atmospheric pressure and was recovered unchanged. (C) The acid (7·8 g.), dissolved in toluene (50 c.c.), was heated on the steam-bath, and phosphoric oxide (20 g.) added in portions. After 3 hours, water was added, the toluene later separated, dried, and evaporated under reduced pressure, and the product distilled. The oil (2 g.) collected at 140—160°/18 mm. solidified to a colourless solid, m. p. 105—115°. Much high-boiling material was obtained. The solid, dissolved in ether, was washed several times with sodium carbonate solution, dried, and evaporated. Only a few mg. of oil were obtained. The sodium carbonate solution on acidification gave the unchanged phenylacetic acid, m. p. 124°.

iso*Coumaranone.*—2-Acetoxybenzylidene azlactone (67 g.) (Erlenmeyer and Stadlin, *Annalen*, 1904, **337**, 290) was boiled under reflux with 10% sodium hydroxide (670 c.c.) for 5 hours, filtered, cooled in ice, treated with 6% hydrogen peroxide (650 c.c.), and left overnight. Addition of hydrochloric acid precipitated the phenylacetic acid and benzoic acid which were isolated with ether and distilled. The fraction (44 g.), b. p. 240—260°, a yellow oil solidifying to a paste, was taken up in ether, washed repeatedly with sodium carbonate solution, and dried. After removal of the ether, the product was distilled under reduced pressure. *iso*Coumaranone (20 g.) was collected at 144°/35 mm., n^{20} 1·547.

Alkylation of iso*Coumaranone with Diethylaminoethyl Chloride.*—*iso*Coumaranone (3·5 g.) and diethylaminoethyl chloride (3·6 g.) were stirred in toluene (30 c.c.) in an atmosphere of nitrogen. Pulverised sodamide (1·25 g.) was added with cooling. After addition of the sodamide, the temperature was raised slowly to 90° and maintained there for 2 hours. The mixture was heated at 100° for 2 hours and finally boiled under reflux for 2 hours. The solution was washed with water and extracted with hydrochloric acid. The acid extract was basified, and the amine isolated with ether and fractionated. *2-Diethylaminoethoxyphenylacetamide* (3·8 g.) was collected at 168—172°/0·05 mm. as a yellow oil, crystallising in square plates on standing. On slow evaporation of its ethereal solution, the amide crystallised in colourless prisms, m. p. 75° (Found: C, 67·1; H, 8·7; N, 11·4. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8; N, 11·2%). The product evolves nitrogen with nitrous acid.

*3-Morpholino*iso*coumaranone.*—*iso*Coumaranone (1·3 g.) and ice chips were shaken, and bromine (1·6 g.) was added dropwise. When the colour of the bromine had disappeared, the product was taken up in ether and washed several times with water. Morpholine (1·8 g.) was added to the dried ethereal layer, and the whole left overnight. Hemispherical clusters of crystals separated and were collected. The *3-morpholino*iso*coumaranone hydrobromide* crystallised from ethanol in colourless plates (0·5 g.), m. p. 171° (decomp.) (Found: C, 48·4; H, 5·0; N, 5·0. $C_{12}H_{13}O_2N$,HBr requires C, 48·0; H, 4·7; N, 4·7%).

2-Methoxybenzyl Alcohol.—2-Methoxybenzaldehyde (10 g.) was hydrogenated over platinum oxide catalyst (0·05 g.) activated with ferrous sulphate (0·5 c.c. of 0·1M.) in ethanol solution (50 c.c.) at atmospheric pressure. When the calculated amount of hydrogen had been absorbed, the catalyst was centrifuged and used again with more of the aldehyde (11 g.). The combined alcoholic solutions were evaporated and distilled. The alcohol (20·5 g.) was collected at 135°/22 mm.

2-Methoxybenzyl Bromide.—Prepared according to Lapworth and Shoesmith (*J.*, 1922, **121**, 1396), this bromide, b. p. 112°/12 mm., frequently polymerised on distillation, so the crude compound was used for conversion into the nitrile.

2-Methoxybenzyl Cyanide (cf. Pschorr, Wolfe, and Buckow, *Ber.*, 1900, **33**, 166).—The crude undistilled bromide (38 g.) was boiled under reflux for 1 hour with potassium cyanide (15 g.), ethanol (150 c.c.), and water (25 c.c.). Water was added, the ethanol distilled under reduced pressure, and the cyanide isolated with ether and distilled. It was collected as a colourless oil, b. p. 130—140°/14 mm., solidifying to a colourless solid (19·2 g.). On crystallising from benzene–ligroin it formed thin prisms, m. p. 67°.

α-(β-Diethylaminoethyl)-2-methoxybenzyl Cyanide.—2-Methoxybenzyl cyanide (4·9 g.) was stirred with diethylaminoethyl chloride (6·0 g.) and toluene (50 c.c.). Sodamide (1·6 g.) was added in portions, and the temperature raised slowly to 75°. After 3 hours, the temperature was further raised to 100° for 1½ hours and finally the mixture was boiled under reflux for 1½ hours. The toluene layer was washed with water and extracted with hydrochloric acid. The extract was basified, and the product isolated with ether and distilled. The cyanide (5·3 g.), a colourless oil, was collected at 122°/0·04 mm. The *oxalate* crystallised from ethanol in colourless, glistening plates, m. p. 169° (gas evolution) (Found: C, 60·85; H, 7·2. $C_{15}H_{22}ON_2,C_2H_2O_4$ requires C, 60·7; H, 7·1%).

Ethyl 2-Methoxy-α-(β-diethylaminoethyl)phenylacetate.—The above cyanide (11 g.) was boiled under reflux for 8 hours with 18% hydrochloric acid, evaporated to dryness under reduced pressure, and the residue taken up in ethanol and filtered from the ammonium chloride. The filtrate was evaporated, leaving a viscous brown syrup of the amino-acid hydrochloride. This was dried by heating in a vacuum and esterified with alcoholic hydrogen chloride. The solvent having been distilled, the residue was dissolved in water, basified with sodium carbonate solution, and the *amino-ester* isolated with ether and distilled. The base (7·1 g.), a colourless oil, was collected at 122—128°/0·15 mm., and on redistillation had b. p. 125°/0·13 mm (Found: C, 69·5; H, 9·3. $C_{17}H_{27}O_3N$ requires C, 69·6; H, 9·2%).

*3-β-Diethylaminoethyl*iso*coumaranone.*—The alkylated benzyl cyanide was boiled under reflux for 1¼ hours with 3 parts of glacial acetic acid and 8 parts of hydrobromic acid (*d* 1·5); the solvents were evaporated off under reduced pressure and the semicrystalline paste was dissolved in ethanol, filtered from ammonium bromide, and evaporated. The residual syrup gave a violet ferric chloride colour and a red coloration with benzenediazonium chloride, and consisted presumably of the phenolic amino-acid hydrobromide. The syrup (7·8 g.) was evaporated to dryness with pulverised fused sodium acetate (2·5 g.) and ethanol and then heated at 120° under reduced pressure for 1 hour. On raising the bath temperature to 180°, a yellow oil distilled at 11 mm. and was collected and redistilled. The diethylaminoethyl*iso*coumaranone (4·0 g.), a pale yellow oil, was collected at 166°/10 mm. The *picrate* crystallised from ethanol in yellow, rhombic prisms, m. p. 149° (Found: C, 51·9; H, 4·9; N, 12·0. $C_{14}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 51·9; H, 4·8; N, 12·1%).

2 : 3-Dimethoxybenzaldehyde.—From *o*-vanillin (100 g.), sodium hydroxide solution (300 c.c. of 20%), and methyl sulphate (120 g.), following the directions of Rupp and Linck (*Arch. Pharm.*, 1915, **235**, 35), the dimethoxybenzaldehyde (73 g.), b. p. 132°/12 mm., was obtained, and from the mother-liquors unchanged *o*-vanillin (21 g.) was recovered. By using *o*-vanillin (100 g.), 20% sodium hydroxide (450 c.c.), and methyl sulphate (180 g.) the yield was raised to 89 g., *o*-vanillin still being recovered.

2 : 3-*Dimethoxybenzylidenerhodanine.*—2 : 3-Dimethoxybenzaldehyde (84 g.), rhodanine (68 g.) (Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1127), and glacial acetic acid (340 cc.) were boiled under reflux, and fused sodium acetate (126 g.) was added. The mixture rapidly set to an orange paste. After 30 minutes, addition to water precipitated the *benzylidenerhodanine* (121 g.), which was collected, washed with water, a little ethanol, and finally with ether. The analytical specimen crystallised from ethanol in radiating clusters of fine, lemon-yellow needles, m. p. 209° (Found : C, 51·3; H, 4·2; N, 5·45. $C_{12}H_{11}O_3NS_2$ requires C, 51·3; H, 3·9; N, 5·0%). The product has peculiar electrical properties. It adheres tenaciously to objects, and transference from one vessel to another causes it to scatter in all directions.

2 : 3-*Dimethoxyphenylthiopyruvic Acid.*—The crude benzylidenerhodanine (105 g.) was divided into three batches of 35 g. and each was hydrolysed by heating for 30 minutes in the steam-bath with 15% sodium hydroxide solution (160 c.c.). Cooling in a freezing mixture and rapid addition of cooled 10% hydrochloric acid (160 c.c.) precipitated the *thiopyruvic acid*; it crystallised on standing to a buff-coloured solid, m. p. 118—124°, which was collected and washed with water. (Combined yield 89 g., 99%.) The analytical specimen crystallised from methanol in small, pale yellow needles, m. p. 134° (Found : C, 55·2; H, 5·3. $C_{11}H_{12}O_4S$ requires C, 55·0; H, 5·0%).

2 : 3-*Dimethoxybenzyl Cyanide.*—(A) Hydroxylamine hydrochloride (16·2 g.), dissolved in warm water (15 c.c.), was added to a solution of sodium (5·4 g.) in ethanol (155 c.c.). The sodium chloride having been filtered off, the filtrate was added to the thiopyruvic acid (18 g.) and the mixture boiled under reflux for 20 minutes. The ethanol was removed and the residue taken up in dilute sodium hydroxide solution (39 c.c. of 5%). The sulphur was filtered off, and the filtrate cooled in a freezing mixture and cautiously acidified with 10% hydrochloric acid (39 c.c.). The oximino-acid was precipitated as a viscous yellow syrup which was isolated with ethyl acetate. The crude acid was treated with acetic anhydride (60 c.c.) and heated on the steam-bath for 10 minutes. The acetic anhydride was removed under reduced pressure, and the residue taken up in ether, washed with sodium carbonate solution, dried, and evaporated. The remaining brown oil was distilled, and the cyanide (3·8 g.) collected at 148°/11 mm. (Found : C, 67·4; H, 6·1. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%).

(B) 2 : 3-Dimethoxybenzyl alcohol (54 g.) (prepared by reduction of the aldehyde with formaldehyde and aqueous methanolic sodium hydroxide; cf. Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905), dissolved in benzene (100 c.c.), was converted into the bromide with hydrogen bromide, the reaction being carried out in a freezing mixture, and without purification the crude bromide was dissolved in ethanol (240 c.c.) and boiled under reflux for 1½ hours with a solution of potassium cyanide (24 g.) in water (40 c.c.). Water was added, the ethanol evaporated under reduced pressure and the cyanide isolated with ether and distilled. The product (41 g.) was collected at 152°/12 mm. On standing, it crystallised in fine white needles, m. p. 20—21°.

4-*Cyano*-4-(2′ : 3′-*dimethoxyphenyl*)-1-*methylpiperidine.*—An aqueous solution of *N*-methyl-2 : 2′-dichlorodiethylamine hydrochloride (26 g.) was cooled and treated with the calculated amount of sodium hydroxide solution and with saturated potassium carbonate solution, and the free base extracted several times with toluene (total volume, 350 c.c.). The dried (K_2CO_3) toluene layer and 2 : 3-dimethoxybenzyl cyanide (25 g.) were stirred and cooled during the gradual addition of sodamide (10·8 g.). When heat evolution had ceased, the mixture was heated for 1 hour at 70°, 2 hours at 85°, 1 hour at 100°, and finally boiled under reflux for 2 hours. The solution was washed with water and extracted with hydrochloric acid, and the acid layer basified. The liberated amine was isolated with toluene and fractionated in a vacuum. The piperidine (5·6 g.), a colourless oil, was collected at 168—175°/0·2 mm. On keeping, it crystallised in colourless rods, m. p. 96°. The picrate crystallised from much ethanol in microscopic, yellow needles, m. p. 194° (Found : C, 51·8; H, 4·9; N, 14·4. Calc. for $C_{15}H_{20}O_2N_2,C_6H_3O_7N_3$: C, 51·5; H, 4·7; N, 14·3%). Care must be taken to protect the lungs and skin during operations with the dichlorodiethylmethylamine.

4-*Carboxy*-4-(2′ : 3′-*dihydroxyphenyl*)-1-*methylpiperidine.*—The above cyanide (2·2 g.) was boiled under reflux for 2½ hours with hydrobromic acid (20 c.c., *d* 1·5). The acid was evaporated under reduced pressure and the crystalline residue crystallised from ethanol. The *phenylpiperidinecarboxylic acid hydrobromide* (2·2 g.) was obtained in colourless needles, m. p. 272·5° (Found : C, 47·4; H, 5·6; N, 4·5. $C_{13}H_{17}O_4N,HBr$ requires C, 47·0; H, 5·4; N, 4·2%).

7-*Acetoxy*-3-spiro-(*N*-*methyl*-4′-*piperidyl*)*iso*coumaranone.—The above acid (0·8 g.) was boiled under reflux for 3 hours with acetic anhydride (10 c.c.), acetic acid (3 c.c.), and fused sodium acetate (1·0 g.). The solvents were distilled under reduced pressure, and the residue taken up in water and basified with sodium carbonate solution. The liberated amine was isolated with ether and distilled in bulbs. The *spiro*piperidino*iso*coumaranone (0·32 g.), a colourless glass, was collected at 150°/0·07 mm. It crystallised, on keeping, in colourless rhombic plates. The *oxalate* crystallised from ethanol in clusters of colourless needles, m. p. 196° (Found : C, 55·5; H, 5·5; N, 3·8. $C_{15}H_{17}O_4N,C_2H_2O_4$ requires C, 55·9; H, 5·2; N, 3·8%). The *picrate* crystallised from much ethanol in yellow rhombic platelets, m. p. 250° (decomp.) (Found : C, 48·9; H, 4·2. $C_{15}H_{17}O_4N,C_6H_3O_7N_3,H_2O$ requires C, 48·3; H, 4·2%).

The author thanks Sir Robert Robinson for suggesting this work, and for the interest he has taken in it. He is also grateful to Imperial Chemical Pharmaceuticals, Ltd., for kindly testing the analgesic properties of some of the substances described herein. The results of the pharmacological tests will be published elsewhere.

Dyson Perrins Laboratory, Oxford. [*Received, December 3rd,* 1945.]

NOTES.

An Improved Method of Nitrating Aromatic o-*Hydroxy-carboxylic Acids and their Esters.*

By H. C. Barany and M. Pianka.

The following modification appears to be an improvement on the methods stated in the literature (Huebner, *Annalen*, 1879, **195**, 7; Deninger, *J. pr. Chem.*, 1905, **42**, 550; Hirsch, *Ber.*, 1900, **33**, 3239; Meldola, Foster, and Brightman, *J.*, 1917, **111**, 536; Raiziss and Proskouriakoff, *J. Amer. Chem. Soc.*, 1922, **44**, 791; Meldrum and Hirve, *J. Indian Chem. Soc.*, 1928, **5**, 95; Gough and King, *J.*, 1930, **137**, 686; Baroni and Kleinau, *Monatsh.*, 1936, **68**, 258; Koenig, *Ber.*, 1890, **23**, 806; Dye, *J.*, 1915, **107**, 1625) for nitrating aromatic *o*-hydroxy-carboxylic acids and their esters. It employs as nitration agent a 10% solution of nitric acid (*d* 1·42) in glacial acetic acid. Distillation of this mixture afforded a fraction, b. p. 128—130°, which seemed to be diacetylorthonitric acid (Pictet, *Chem. Zentr.*, 1902, II, 1438; *Ber.*, 1902, **35**, 2526). The procedure was to dissolve 1 mole of the compound in the smallest amount of glacial acetic acid and add rapidly, at room temperature, a mixture of 1 mole of nitric acid (*d* 1·42) in 9 times its volume of glacial acetic acid, then warm the reaction mixture until it became brown, cool it, and precipitate the nitro-compound with excess of water. In all cases except in that of 2-hydroxy-3-naphthoic acid the nitro-group was found to be in a position *para* to the hydroxyl group.

The following were prepared: 5-Nitrosalicylic acid, white needles from water, m. p. 228° (yield, 41%); methyl 5-nitrosalicylate, white needles from ether, m. p. 96° (yield, 51%); ethyl 5-nitrosalicylate, obtained from the reaction mixture on standing, yellow needles, m. p. 98—99° (yield, 64%); 4-nitro-1-hydroxy-2-naphthoic acid, pale yellow needles from dilute acetone, m. p. 214° (yield, 69·5%); 4-nitro-3-hydroxy-2-naphthoic acid, orange crystals from ether, m. p. 233—234° (yield, 49%); methyl 4-nitro-1-hydroxy-2-naphthoate, pale yellow needles from benzene, m. p. 161° (yield, 77·3%); *ethyl 4-nitro-1-hydroxy-2-naphthoate*, pale yellow needles from benzene, m. p. 87—88° (yield, 86%) (Found: C, 59·82; H, 4·13; N, 5·41. $C_{13}H_{11}O_5N$ requires C, 59·77; H, 4·21; N, 5·36%); *propyl 4-nitro-1-hydroxy-2-naphthoate*, pale yellow needles from benzene–light petroleum, m. p. 117—118° (yield, 87%) (Found: C, 60·87; H, 4·82; N, 5·00. $C_{14}H_{13}O_5N$ requires C, 61·09; H, 4·72; N, 5·09%).

Melting points are uncorrected.—RESEARCH LABORATORIES, DUFAY-CHROMEX LIMITED, ELSTREE, HERTS. [*Received, April 5th*, 1946.]

Amides Derived from ω-Chloroacetophenone. By WILLIAM A. WATERS.

THE water-soluble aromatic amines derived from ω-chloroacetophenone have a pungency which is not unlike that of capsaiacin. Since the maximum pungency in the acylvanillylamide (capsaiacin) series is found in an amide of one particular chain-length (compare Ford-Moore and Phillips, *Rec. Trav. chim.*, 1934, **53**, 847), it was of interest to prepare a number of acylamido-ω-chloroacetophenones, and to investigate both their lachrymatory characters and their pungency in aqueous solution. Both these properties, however, decreased as the chain-length of the amide increased. The following *compounds* were prepared, by standard methods, in the course of this investigation.

ω-Chloro-4-acylamidoacetophenones.

		Analyses.					
		Found.			Required.		
Acyl group.	M. p.	C, %.	H, %.	Cl, %.	C, %.	H, %.	Cl, %.
Propionyl	208°	58·4	5·33	16·0	58·5	5·32	15·7
n-Butyryl	178	60·0	5·86	14·9	60·1	5·85	14·8
*iso*Butyryl	149	60·2	6·08	14·3	60·1	5·85	14·8
n-Valeryl	175	61·6	6·29	14·4	61·5	6·31	14·0
*iso*Hexoyl	171	63·8	7·11	12·9	62·8	6·73	13·3
n-Octoyl	127	65·0	7·70	12·0	65·1	7·46	12·0
n-Pelargonyl	116	65·7	7·75	11·8	65·9	7·81	11·5
n-Lauryl	114	69·0	8·4	9·6	68·3	8·53	10·1
Myristyl	119	70·1	9·14	9·49	69·6	8·96	9·34
Stearyl	111	71·1	9·91	8·6	71·5	9·64	8·1
Undecenoyl	105	68·4	7·39	10·7	68·0	7·75	10·6
β-Chloropropionyl	201	50·4	4·47	27·0	50·8	4·23	27·3

ω-Chloro-3-acylamidoacetophenones.

		Analyses.					
		Found.			Required.		
Acyl group.	M. p.	C, %.	H, %.	Cl, %.	Cl, %.	H, %.	Cl, %.
Propionyl	136°	58·8	5·87	15·5	58·5	5·33	15·7
n-Butyryl	93	60·4	5·82	15·1	60·1	5·85	14·8
*iso*Butyryl	136	60·3	5·65	14·8	60·1	5·85	14·8
n-Valeryl	95	61·9	6·52	14·1	61·5	6·31	14·0
*iso*Hexoyl	106	62·9	6·8	13·6	62·8	6·73	13·3
n-Octoyl	96	65·1	7·40	11·7	65·1	7·46	12·0
n-Pelargonyl	91	66·1	7·73	11·5	65·9	7·81	11·5
n-Lauryl	96	68·6	8·89	9·84	68·6	8·53	10·1
Myristyl	100	70·3	9·8	8·9	69·6	8·96	9·3
Undecenoyl	92	68·1	7·96	11·1	68·0	7·75	10·6
β-Chloropropionyl	145	50·7	4·23	27·1	50·8	4·23	27·3

The Chief Scientific Officer of the Ministry of Supply is thanked for permission to publish this Note.—CHEMICAL DEFENCE RESEARCH DEPARTMENT, MINISTRY OF SUPPLY. [*Received, February 14th*, 1946.]

Synthesis of Acenaphthene. Part II. By ALEXANDER SCHÖNBERG, RADWAN MOUBASHER, and AKILA MOSTAFA.

SCHÖNBERG and Moubasher (*J.*, 1939, 1429) have shown that, when diphenyl triketone is heated with anhydrous aluminium chloride and the reaction product decomposed with dilute hydrochloric acid, benzil is obtained.

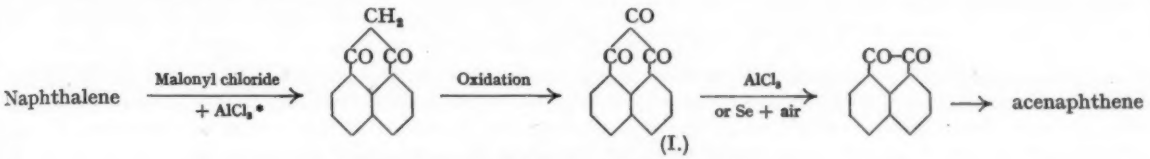
We have now found that benzil can also be obtained from diphenyl triketone by heating it with selenium in the presence of air, and, further, that acenaphthenequinone is obtained when *peri*naphthanetrione (I) is treated with either aluminium chloride or selenium in the presence of air.

Schönberg (*Ber.*, 1921, **54**, 2838) has shown that acenaphthene can easily be obtained from acenaphthenequinone disemicarbazone by the action of sodium ethoxide; we are therefore now able to advance an easy way of preparing acenaphthene from naphthalene without pyrolysis.

It has been stated (Richter–Anschütz, "Chemie der Kohlenstoffverbindungen," 12th Edition, Vol. II, Part 2, p. 739, Leipzig, 1935) that acenaphthenequinone is easily prepared by the action of oxalyl chloride on naphthalene in the presence of aluminium chloride. The above paper of Schönberg (*loc. cit.*) is given as authority for this statement; it is, however, true only for derivatives of acenaphthenequinone.

Action of selenium in the presence of air on peri*naphthanetrione hydrate.* 0·4 G. of the hydrate (Errera, *Gazzetta*, 1913, **43**, 583) was mixed with 1·5 g. of precipitated selenium (Kahlbaum) in a test tube (25 cm. long) and heated in an oil-

bath kept at 250°. Heating was continued for two hours, during which a stream of air was constantly passed through a delivery tube which almost touched the surface of the reaction mixture. Acenaphthenequinone sublimed (60% yield). The crude product was identified after recrystallisation by m. p. and mixed m. p. with an authentic specimen, and also by m. p. and mixed m. p. of the condensation products of *o*-phenylenediamine with the reaction product and with an authentic sample of acenaphthenequinone.



* Fleischer and Retze, *Ber.*, 1922, **55**, 3280.

Action of aluminium chloride on peri*naphthanetrione* (I). A mixture of 5 g. of pulverised anhydrous aluminium chloride and 1 g. of *peri*naphthanetrione (Errera, *loc. cit.*) was heated in a long test tube closed with a calcium chloride tube (bath temperature, 220°). A sublimate was formed, and after 30 minutes was put back into the reaction mixture. 30 Minutes later, the contents of the tube were cooled, treated with ice-cold dilute hydrochloric acid, and left for 12 hours. The solid product was washed with water, dried, and crystallised from toluene. Acenaphthenequinone (yield, 0·3 g.) was identified as above.

Action of selenium in the presence of air on diphenyl triketone. The experiment was carried out as in the case of *peri*-naphthanetrione hydrate, using 0·5 g. of diphenyl triketone and 4 g. of selenium. The reaction product formed long needles on the cooler part of the reaction vessel, and without crystallisation melted at 95°. The mixed m. p. (with a sample of benzil) was not depressed.—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, March 26th*, 1946.]

Substitution.

THE TILDEN LECTURE, DELIVERED IN LEEDS ON NOVEMBER 26TH, 1945, AND IN LONDON ON JANUARY 17TH, 1946.

By E. D. HUGHES, D.Sc., PH.D., F.R.I.C.

THE study of substitution reactions had an early origin and has held a prominent position in the development of the chemistry of carbon compounds. The subject is an extensive one and in order to reduce it to accessible limits we shall deal mainly with recent advances regarding the kinetics and mechanism of substitution, and especially of certain types of replacement reactions occurring at a saturated carbon atom, *e.g.*, $Y + R{-}X \longrightarrow Y{-}R + X$, where Y is an atom or group which can replace a similar entity X in a molecule R—X, R being an organic radical which is saturated at the point of attachment of X. The importance of the kinetic method in the study of mechanism was foreshadowed by the work of Lapworth, Orton, and others in the early years of the present century. More recently, it has played a notable part in the rapid development which the theory of organic reactions has undergone since the enunciation of the electronic theory of valency.

The interest attached to the problem may be said to be two-fold. First, substitution processes are amongst the most common and useful of chemical reactions, and knowledge concerning their mechanism is itself of prime importance. Secondly, a substitution reaction of the type illustrated may be regarded as a comparatively simple unit process and a fruitful attack on the problem by the kinetic and other methods cannot fail to be of value as a guide and a model for the study of other changes. Though often of a seemingly complex character, many reactions can be analysed into stages, which, with regard to kinetics and mechanism, frequently bear some resemblance to a simple replacement process. On the basis of this two-fold definition of objectives, further discussion will be divided into two main sections, comprising (*a*) general principles of aliphatic substitution, and (*b*) applications of general principles.

A. GENERAL PRINCIPLES OF ALIPHATIC SUBSTITUTION.

I. *Historical Survey.*

In the early days of the development of chemical theories, the main question regarding the mechanism of substitution processes was put in the following form : " Is substitution always preceded by addition ? " In a reaction of the type $Y + R{-}X \longrightarrow Y{-}R + X$, where one bond is formed and one is broken, it is obvious that the process could be initiated either by the attack of the reagent (Y) on the molecule R—X (a process tending to form the new bond Y—R first and leading to the expulsion of X), *e.g.*,

$$Y{\cdots}R{-}X \longrightarrow Y{-}R + X,$$

or, alternatively, by the preliminary fission of the R—X bond (followed by the union of Y with R) :

$$R{-}X \longrightarrow R + X;\ Y + R \longrightarrow Y{-}R.$$

Thus there emerged two types of theories of substitution reactions. One postulated addition as an essential condition for the expulsion of the group replaced; the other assumed that the primary dissociation of bonds was involved. In rudimentary form these theories had, as already implied, quite an early origin. It is not proposed to trace that origin fully at this time, but it is of interest to recall that notable advances in the development of more precise views concerning substitution reactions were made through the great impetus both to practical and to theoretical work which resulted from the discovery by Walden in 1895 of the configurational inversion which bears his name.

The first type of theory, which may be called the " addition-complex " theory, was particularly prominent in connection with the problem of the Walden inversion, which was considered from the mechanistic point of view by Fischer, Werner, Pfeiffer, Gadamer and others about the year 1911. In the early versions of the theory it was not clear how the addition took place; it was customary to speak rather vaguely of a union dependent on the " residual affinity " of the reactive carbon atom, and so on, and it is obvious that there were difficulties regarding the valency of this carbon atom, which was already saturated before the attachment of the entering atom or group. These difficulties were dispelled by the idea that addition is not previous to but synchronises with dissociation. This was first stated in an acceptable form by G. N. Lewis (" Valence and the Structure of Atoms and Molecules," 1923, p. 113). The physical basis (including the stereochemical implications) of the synchronous mechanism has been discussed by Polanyi (see especially Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164; Bergmann, Polanyi, and Szabo, *ibid.*, 1933, **20**, 161; *Trans. Faraday Soc.*, 1936, **32**, 843), and by Olson (*J. Chem. Physics*, 1933, **1**, 418; Olson and Long, *J. Amer. Chem. Soc.*, 1934, **56**, 1294; 1936, **58**, 393), particularly in relation to the application of the mechanism to the reaction between an anion and a neutral molecule (see also later references to the work of these authors).

With regard to the second type of theory (the " prior dissociation " theory), development has also taken place in the direction of greater precision in its formulation; the theory has evolved, from a stage at which little attempt was made to explain how the replaced group was expelled, to its position at the present time,

when we distinguish between various types of fission and specify quite precisely the circumstances in which each type will function (see Section II below).

The impression that the two types of theories were incompatible (in the sense that no degree of application could be given to both) has also undergone revision. By detailed reference to certain reactions which may be labelled " Nucleophilic Substitutions " we shall show that our present views regarding the mechanism of such processes may be said to embody the acceptable versions of both (*i.e.*, the " addition-complex " and the " prior dissociation ") theories. The concept of the duality of mechanism in substitution reactions at a saturated carbon atom has in fact become the main feature of the recent developments, which we shall now discuss.*

It is necessary first to arrive at a classification of substitution types, as indicated immediately below.

II. *Types of Substitution.*

In a substitution reaction of the general form $Y + R{-}X \longrightarrow Y{-}R + X$, it is clear that, independently of mechanism, the R–X bond must be severed in the course of reaction. There are two principal ways by which this can be accomplished, one of which requires further classification into two sub-types (cf. Ingold, *Trans. Faraday Soc.*, 1938, **34**, 227; Hughes, *ibid.*, 1941, **37**, 604). This is represented schematically in the formulæ below, where the dots represent electrons and the vertical lines illustrate the mode of fission of the bond :

$R|\cdot\cdot X$ (1*a*) and $R\cdot\cdot|X$ (1*b*) $\qquad R\cdot|\cdot X$ (2)

Dissymmetric or heterolytic fission. Symmetric or homolytic fission.

In one case, splitting of the bond occurs so that both the bond electrons separate with one of the fragments. In the other, each fragment appropriates one electron. The first type of fission is called dissymmetric or heterolytic fission, and the second is termed symmetric or homolytic fission. The question as to which of these forms will be operative in a given case will depend not only on the natures of R and X but also on the substituting agent and the experimental conditions.† The heterolytic type of fission is characteristic of a large proportion of substitution reactions in solution, which generally involve ions, or entities which readily form ions. Two principal factors determine which of the alternative sub-types will be followed (see Table below). The first is whether the natures of R and X are such that the expelled group X (we suppose that the substitution is to take place at R) tends to separate with its electrons (1*a*, *e.g.*, halogen in alkyl halides) or without its electrons (1*b*, *e.g.*, hydrogen in suitably activated C–H bonds), and the second is whether the substituting agent uses its electrons to attack the nucleus of R (1*a*, *e.g.*, $H\bar{O}$ or $R_3N\colon$) or uses its nucleus to combine with the electrons of R (1*b*, *e.g.*, H^+ or D^+). The former type of substituting agent is termed " nucleophilic " and the latter " electrophilic " and the substitution processes are named accordingly.

Replacement reactions of the homolytic type (2) obtain under conditions favourable to the existence of atomic or other neutral reagents and when there is little tendency for ionic fission in the R—X bond; they are thus common in gas-phase reactions [*e.g.*, the photo-halogenation (by halogen atoms) of paraffinic hydrocarbons in the gaseous phase].

Our main discussion will be confined to reactions of the heterolytic type.

Types of Substitution.

(1) *Heterolytic.*

(*a*) *Nucleophilic.*

$$Y\colon + R|\colon X \longrightarrow Y\colon R + \colon X \ (S_N)$$

(*e.g.*, $H\bar{O} + R{-}Cl \longrightarrow HO{-}R + \bar{C}l$)

(*b*) *Electrophilic.*

$$Y + R\colon|X \longrightarrow Y\colon R + X \ (S_E)$$

(*e.g.*, $D^+ + R{-}H \longrightarrow D{-}R + H^+$)

(2) *Homolytic.*

$$Y\cdot + R\cdot|\cdot X \longrightarrow Y\colon R + \cdot X$$

(*e.g.*, $Cl\cdot + R{-}H \longrightarrow Cl{-}R + \cdot H$)

For convenience in reference the nucleophilic and electrophilic types of substitution are labelled S_N and S_E

* For the detailed description of the development of the general theory, see especially the following papers : Hughes and Ingold, *J.*, 1935, 244; Hughes, Ingold, and Shapiro, *J.*, 1936, 225; Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185, 202; Bateman, Cooper, Hughes, and Ingold, *J.*, 1940, 925; Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603. In connection with special points, reference to specific sections of these, and to other relevant papers, will be made in the following pages.

† The nature of the substituting agent is particularly important when it participates in a one-stage process (bimolecular mechanism, see below). When a preliminary rate-determining fission of the R–X bond is involved (unimolecular mechanism) the nature of the primary dissociation is determined independently of the substituting agent, which, nevertheless, must intervene in the formation of the substitution product.

respectively (Gleave, Hughes, and Ingold, *J.*, 1935, 236). Our attention will now be directed to the nucleophilic type, which has been more extensively studied from the mechanistic standpoint.

In nucleophilic substitution, there is a transfer of electrons from Y to R and from R to X. The reagent may therefore be either negative or neutral (provided it has unshared electrons) and the replaceable group may be either neutral or positive. Four cases thus arise, which may, for the most part, be illustrated by examples of familiar reactions in organic chemistry :

(1) Y negative and X neutral, *e.g.*, $\overline{HO} + R{-}Br \longrightarrow HO{-}R + \overline{Br}$

(2) Y negative and X positive, *e.g.*, $\overline{Br} + R{-}\overset{+}{N}R_3 \longrightarrow Br{-}R + NR_3$

(3) Y neutral and X neutral, *e.g.*, $R_3N + R{-}Br \longrightarrow R_3\overset{+}{N}{-}R + \overline{Br}$

(4) Y neutral and X positive, *e.g.*, $R_3N + R{-}\overset{+}{S}R_2 \longrightarrow R_3\overset{+}{N}{-}R + SR_2$

The examples refer to (1) the hydrolysis of alkyl halides, (2) the decomposition of alkylammonium salts, (3) the formation of alkylammonium salts from tertiary amines and alkyl halides, (4) the formation of alkylammonium cations from tertiary amines and alkylsulphonium cations.

III. *Duality of Mechanism in Nucleophilic Substitution.*

We now recognise two operative mechanisms for these substitution processes. For the sake of clarity in presentation we shall first describe the mechanisms and then proceed to outline the principal observations which present strong reasons for adopting the theory of the duality of mechanism in nucleophilic substitution.

The first mechanism is a one-stage mechanism, involving a synchronous electron transfer from Y to R and from R to X, *e.g.*,

$$Y{:}\curvearrowright R{-}\overset{\curvearrowright}{X} \longrightarrow Y{-}R + {:}X \quad (S_N2)^*$$

$$\text{Example : } \overset{-\bullet}{HO} + R{-}Cl \longrightarrow \overset{\sim -e/2}{HO}\cdots\cdots R\cdots\cdots\overset{\sim -e/2}{Cl} \longrightarrow HO{-}R + \overset{-\bullet}{Cl}$$

Initial state. Transition state. Final state.

Since both reactants are simultaneously involved, this mechanism is termed " bimolecular "; the numerical part of the designation (S_N2) is intended to symbolise this character. As an example, we may take the bimolecular alkaline hydrolysis of an alkyl halide. The anionic charge ($-e$), initially on the entering group and finally on the expelled group, becomes distributed in the transition state as indicated in the schematic representation.

The second mechanism is a two-stage process, wherein a rate-determining ionisation is succeeded by a reaction between the carbon cation formed and the substituting agent, *e.g.*,

$$\left.\begin{array}{l} R{-}\overset{\curvearrowright}{X} \xrightarrow[\text{slow}]{} \overset{+}{R} + {:}X \\ Y{:}\curvearrowright\overset{+}{R} \xrightarrow[\text{rapid}]{} Y{-}R \end{array}\right\} (S_N1)$$

$$[\text{Example : } R{-}Cl \longrightarrow \overset{\delta+}{R}\cdots\cdots\overset{\delta-}{Cl} \longrightarrow \overset{+}{R} + \overline{Cl} \text{ (slow), followed by } \overset{+}{R} + \overline{OH} \longrightarrow R{-}OH \text{ (rapid).}]$$

In the unimolecular hydrolysis of an alkyl halide, for example, there is a partial separation of charges in the transition state of the rate-determining ionic dissociation, which is followed by a rapid reaction between the carbon cation and a hydroxide ion. Although the importance of solvation in ionic dissociation is recognized, this mechanism is termed " unimolecular " because only one reactant, R—X, is undergoing covalency change in the rate-determining stage. The numerical part of the designation S_N1 again indicates the molecularity of this mechanism.

The two mechanisms should clearly be characterised by distinctive kinetics and this, together with other significant properties, should be useful for purposes of diagnosis. We shall now review the principal evidence which has been derived from a study of the reactions of organic halides. In many instances supporting evidence has been obtained from parallel investigations of the reactions of ammonium or sulphonium salts.

IV. *Evidence for the Duality of Mechanism.*

(1) *Energy Requirements.*—It seems opportune to discuss this question at the outset, since the theory of the assessment of activation energies for simple reactions has reached a stage where it is at least possible to decide whether or not a given mechanism is energetically feasible. For the bimolecular mechanism, the earlier, approximate calculations of London (*Z. Electrochem.*, 1929, **35**, 552) and of Eyring and Polanyi (*Z. physikal. Chem.*, 1931, *B*, **12**, 279) have been adapted and developed for the case of an anion reacting with a neutral

* In this formulation, and elsewhere in this lecture, arrows are used to show the direction of electron displacements. Sign labels on X and Y are omitted because of the various possibilities already mentioned.

molecule by Polanyi and his co-workers (Polanyi, *Proc. Roy. Soc.*, 1934, *B*, **116**, 203; Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 604; Baughan and Polanyi, *ibid.*, 1941, **37**, 648). The calculated activation energies (*e.g.*, for the "halogen-exchange" reaction, $\bar{I} + R{-}Cl \longrightarrow I{-}R + \bar{Cl}$) are found to have easily accessible values and are in fact in good agreement with the experimental results obtained under conditions for which the bimolecular mechanism is considered to be applicable. For the unimolecular mechanism, the position has seemed more controversial, mainly because some authors have given inadequate consideration to solvation effects in ionic dissociation. Olson and Voge (*J. Amer. Chem. Soc.*, 1934, **56**, 1690) objected to mechanisms of this type on the ground that primary dissociation would imply much too large a heat of activation. Hughes and Ingold (*J.*, 1935, 245) met this difficulty by drawing attention to the important part played by facilitating solvation forces in suitable solvents. In an attempt to secure evidence of a quantitative character, Ogg (*J. Amer. Chem. Soc.*, 1939, **61**, 1946) calculated that the activation energies demanded by the unimolecular mechanism would be at least 50 kg.-cals., and therefore too great to admit of measurable rates at ordinary temperatures. His calculations, however, refer primarily to the hydrolysis of the methyl halides, which are most unsuitable structures for the facile operation of the unimolecular mechanism [see sub-section (2) below]. Furthermore, it has been pointed out (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1006) that Ogg's calculations were too rough to be significant, the uncertainties introduced being of the same order of magnitude as the quantities calculated. Finally, Baughan, Evans, and Polanyi (*Trans. Faraday Soc.*, 1941, **37**, 377) deduced a much lower value (~ 30 kg.-cals.) for the activation energy of the ionisation of methyl iodide in water—a value which would accommodate an ionisation mechanism even for this halide.

(2) *The Kinetic Form of the Substitution Reaction.*—In general, the bimolecular mechanism should lead to second-order kinetics (being of the first-order with respect to each reactant), while the unimolecular mechanism should, in first approximation (see below), lead to first-order kinetics, since the substituting agent does not function in the rate-determining stage.* Many cases of each type of kinetic behaviour have been observed (for a full summary see *Trans. Faraday Soc.*, 1941, **37**, 608). In illustration of the kinetic evidence, we shall mention here but one set of observations, which refer to the hydrolysis of alkyl halides with alkali in aqueous alcohol. Kinetic investigations have shown that for certain halides (*e.g.*, the methyl halides) the reaction is of the second order, the rate being dependent on the concentration of the alkyl halide and on that of hydroxide ions. The hydrolysis of certain other halides (*e.g.*, the *tert.*-butyl halides) is, on the other hand, found to be of the first order, the rate being independent of the concentration of hydroxide ions and the same in acid, neutral, and alkaline solution. Evidently, there is a difference of mechanism between the two types and the kinetic observations are entirely consistent with the concept of the duality of mechanism. Many unsuccessful attempts have been made to find other explanations for these kinetic results. An alternative hypothesis that the first-order reactions follow a bimolecular mechanism in which the solvent is acting as the reagent (its presence in large excess accounting for the kinetic order) cannot be entertained, because a nucleophilic substituting agent is acting analogously to a base, and it is inconceivable that water molecules should be effective reagents when the more powerfully basic hydroxide ions are quite inactive.†

Furthermore, if we reduce the water concentration to small proportions comparable with the alkyl halide, then, by varying the concentration in a suitable (ionising) medium, it can be shown that the rate of hydrolysis of the type of halide for which a unimolecular mechanism is postulated is independent of the water concentration (Bateman and Hughes, *J.*, 1937, 1187; 1940, 935; cf. Koskoski, Thomas, and Fowler, *J. Amer. Chem. Soc.*, 1941, **63**, 2451). Several other criteria of mechanism (some of which are described later) have been applied to the first-order hydrolysis of alkyl halides and, in those cases for which the rate is quite independent of hydroxide-ion concentration, the evidence consistently supports an ionisation mechanism (see *Trans. Faraday Soc.*, 1941, **37**, 611). The demonstration that, while the rate of hydrolysis of some alkyl halides is sensitive to alkali, that of others is insensitive, is, without doubt, highly significant, particularly since rational predictions can be made, on the basis of the concept of the duality of mechanism (as will be shown later), concerning the types of structure which exhibit the different kinds of behaviour.

A detailed consideration of the kinetic form of the substitution reaction may provide further evidence of mechanism, particularly for unimolecular reactions, in the following way (we give here only a brief qualitative outline of the method; for a full account of the quantitative treatment see *J.*, 1940, pp. 960, 979, 1011, 1017). As already stated, in first approximation the unimolecular mechanism leads to first-order kinetics. Deviations of a highly characteristic nature may, however, arise if the rate-determining ionisation is reversible under the conditions employed. In the unimolecular hydrolysis of an appropriate alkyl halide in aqueous solvents, *e.g.*,

$$R{-}Cl \underset{(2)}{\overset{(1)}{\rightleftharpoons}} \overset{+}{R} + \bar{Cl} \xrightarrow[(3)]{H_2O} R{-}OH + \overset{+}{H} + \bar{Cl},$$

* We shall throughout employ the expressions "first order" and "second order" to indicate the type of kinetic equation which a reaction follows: the use of the terms "unimolecular" and "bimolecular" will be confined to the description of reaction mechanisms. There is not always a simple and exclusive correspondence between order and mechanism, and the persistent practice in current literature of interchanging and intermixing the two types of nomenclature as if the corresponding terms were completely synonymous is regrettable and confusing.

† This hypothesis was considered in our early discussions but it was found to be an inadequate explanation of our observations (cf. Hughes and Ingold, *J.*, 1935, 249). It was subsequently revived by other authors in attempts to discredit the concept of the duality of mechanism. To avoid misunderstanding, it should be added that we are, of course, aware that water (and alcohol) molecules may under favourable conditions function as substituting agents in a one-stage process; but in these circumstances reagents such as hydroxide ions act more powerfully.

reaction (2) may become of importance in certain circumstances, particularly towards the end of the hydrolysis when the concentration of chloride ions is reaching its maximum value, and this should exert a characteristic effect—a growing retardation of rate—on the kinetic form of the reaction. This deviation from simple first-order kinetics has been observed, and the disturbance shown to be quantitatively in accord with the requirements of the unimolecular mechanism. The bimolecular mechanism, *e.g.*, a one-stage hydrolysis involving solvent molecules as effective reagents, *viz.*,

$$R{-}Cl + H_2O \longrightarrow R{-}OH + \overset{+}{H} + \overset{-}{Cl}\ (S_N2),$$

provides for no such retardation, and no effect of this kind has been observed amongst reactions regarded for other reasons as bimolecular. More elaborate, but highly distinctive evidence of mechanism has been derived from the effect of the addition of a " common-ion " salt, whose anion is identical with that formed from the alkyl halide (*e.g.*, the addition of extraneous chloride ions in the hydrolysis of an alkyl chloride) and also of " non-common-ion " salts, whose anions are different.

The effect just described may be referred to as the " mass-law " effect characteristic of the unimolecular mechanism. There is another influence associated with the presence of saline substances, namely, the " ionic-strength " effect.* In the hydrolysis of organic halides, the two effects are qualitatively opposite and by suitable choice of salts and experimental conditions both can be assessed quite accurately. Owing to the development of charges in the rate-determining stage of the ionisation of an alkyl halide molecule, the unimolecular mechanism may be expected to have a characteristically large " salt " or " ionic-strength " effect. This too has been observed in the hydrolysis of suitable halides. No effect of the same magnitude is found for those hydrolyses which on other evidence are considered to be bimolecular, neither would it be expected.

(3) *Structural and Environmental Effects.*—In the preceding section, it was shown that, in the hydrolysis of alkyl halides, reaction kinetics consistent with the operation of the two mechanisms previously described (S_N1 and S_N2) have been observed in different cases. The argument in favour of the concept of the duality of mechanisms would be further strengthened if the appearance of the two types of kinetic behaviour could be related in a rational manner with the structure of the reactants and the conditions of reaction. Such relationships have in fact been established. The principal evidence, bearing mainly on the effects of changes in the nature of the reagents and the reaction medium, will now be outlined in illustration of the types of relationships which can be shown to exist (for a full summary see especially *Trans. Faraday Soc.*, 1938, **34**, 187; 1941, **37**, 607).

(3, 1) *Effects Depending on the Nature of* R.—(a) *Polar effects.* If a series of alkyl groups or substituted alkyl groups is placed in order of ability to release electrons to the reaction centre, *e.g.*

$$CH_3{-}Br,\ CH_3{\rightarrow}CH_2{-}Br,\ \begin{matrix}CH_3\searrow\\ \ \ \ CH{-}Br,\\ CH_3\nearrow\end{matrix}\ \begin{matrix}CH_3\searrow\\ CH_3{\rightarrow}C{-}Br\\ CH_3\nearrow\end{matrix}$$

it is found that from left to right in the series the rate of hydrolysis in alkaline solution at first diminishes, whilst the kinetics are of the second order; it then passes through a minimum, in the neighbourhood of which we observe a mixture of second- and first-order kinetics, either of which can be brought into prominence by suitable alteration in the concentration of hydroxide ions; finally, the rate rises steeply and the kinetics are those of the first order, the rate being now independent of the hydroxide ions. For hydrolysis with alkali in aqueous alcohol, the critical region of mechanistic change is situated at the *iso*propyl group, but it must be emphasized that the exact location depends on the conditions employed, especially the composition of the medium. The relationship exhibited is of the type to be expected from a change of mechanism near the point of minimum rate. Groups which supply electrons inhibit the approach of the nucleophilic reagent, the presence of which is necessary for reaction by mechanism S_N2 and which has affinity not for electrons but for nuclei, and they facilitate the supply of electrons to the halogen and thus favour the dissociation, which is the rate-determining stage of mechanism S_N1.† Steric factors also contribute to the inhibiting effect of α-methyl substituents on the rate of bimolecular substitution, as will be explained below in connection with a more striking example (cf. Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164; Hughes and Ingold, *J.*, 1935, 246; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 623; Evans and Polanyi, *Nature*, 1942, **149**, 608, 665; Dostrovsky and Hughes, this vol., p. 157 *et seq.*; Dostrovsky, Hughes, and Ingold, *ibid.*, p. 173).

(b) *Steric effects.* Further evidence is obtained from a study of steric factors. We shall deal with this matter briefly since a recent discussion is available for detailed reference (Dostrovsky, Hughes, and Ingold, *loc. cit.*) and some special aspects of the problem are mentioned later in this lecture. The principle involved is as follows : In the transition state of the bimolecular mechanism, wherein the bond-forming properties of the substituent group are engaged in promoting reaction, five groups are wholly or partly attached by covalency forces to a single carbon atom, a circumstance which may give rise to repulsion between the groups. Reactions taking place by this mechanism may therefore be expected to be very sensitive to steric inhibition by substi-

* The polar substance exerts an influence on the reaction rate which, roughly speaking, may be compared to the effect of changing to a more highly solvating (ionising) medium [cf. sub-section (3, 4)].

† Exceptions to the general inhibiting effect of electron-releasing groups on the bimolecular mechanism may occur, *e.g.*, in the neighbourhood of the bimolecular–unimolecular transition region (cf. Hughes, Ingold, and Shapiro, *J.*, 1936, 225) but a difference in the magnitude of the effect on the two mechanisms persists even in these circumstances. In the bimolecular mechanism the effect is a difference, even though the separate terms cannot be associated each exclusively with the formation or rupture of a bond.

tuent groups of appropriate types. Unimolecular reactions on the other hand should never involve the covalent attachment (wholly or partly) of more than four groups to the reactive carbon atom, the additional forces entering in the transition state of the rate-determining stage being of the longer-range electrostatic type associated with solvation; consequently, steric hindrance should be minimised in these reactions.

It is now generally agreed that the most favourable configuration for the transition state of a bimolecular substitution is that in which the entering and leaving groups and the α-carbon atom lie on or near a straight line, the other attached groups being on or near a plane perpendicular to that line. With this model of the transition state as basis, the distances between the centres of the attacking or displaced radicals and the centres of various atoms in the reacting molecule can be calculated, and a consideration of these distances provides an estimate of the importance of the steric factor in different structures. In our recent investigation of the reactions of *neo*pentyl compounds (*e.g.*, $CMe_3 \cdot CH_2Br$), for which a large steric effect can be shown by simple calculation to be involved, it was found that the halides are singularly inert under conditions which lead to second-order kinetics, *i.e.*, when the bimolecular mechanism is evidently operative. Under conditions favourable to the unimolecular mechanism, however, these compounds are moderately reactive. This circumstance makes it possible, under appropriate conditions, to observe a first-order reaction in the hydrolysis of the *neo*pentyl halides in alkaline solution—a result which it is impossible to achieve with other primary halides owing to the incursion of the second-order reaction [cf. sub-section (a) above].

(c) *Effects observed with special forms of* R. Further evidence in support of the concept of the duality of mechanism may be derived from effects observed with special forms of the radical R, particularly effects emerging from an examination of the reaction products under kinetically controlled conditions. We shall discuss two principal cases, namely, (i) those in which R may (if liberated as $\overset{+}{R}$, as in the unimolecular mechanism) undergo rearrangement or participate in some other distinctive product-relationship, (ii) those in which R is asymmetric at the reaction centre, the molecule R—X being optically active.

(i) *Rearrangement effects.* In a qualitative sense, the reaction of an organic halogen compound (or similar structure, *e.g.*, an 'onium cation) with a nucleophilic substituting agent may, in general, be expected to give rise to the same products independently of whether the mechanism is a one-stage bimolecular process or a two-stage unimolecular process involving a preliminary ionisation. Exceptions may, however, arise in the following way : In the bimolecular mechanism the direct attachment of the reagent proceeding synchronously with the expulsion of the replaced group should always give rise to a substitution product in which the group R is the same as in the reactant. When an intermediate carbon cation is formed, however, it may in special cases undergo rearrangement, so that the products formed in a subsequent reaction with the substituting agent may contain a structure which is distinct from that of the reactant. We shall give two examples of the application of this method. In the first there is the possibility of a rearrangement of the Wagner type; in the second an anionotropic change may occur.

The second-order reaction of *neo*pentyl bromide with sodium ethoxide in dry ethyl alcohol gives ethyl *neo*pentyl ether :

$$CMe_3 \cdot CH_2 \cdot Br + EtONa \longrightarrow CMe_3 \cdot CH_2 \cdot OEt + NaBr$$

This is the direct, straightforward substitution of Br by OEt expected in a bimolecular mechanism. The first-order reaction of the same halide in aqueous ethyl alcohol on the other hand gives *tert.*-amyl derivatives (Dostrovsky, Hughes, and Ingold, *loc. cit.*). Whitmore and his co-workers have emphasized that the formation of *tert.*-amyl compounds in some of the reactions of the *neo*pentyl halides is indicative of the transitory formation of the *neo*pentyl cation in these instances (see especially Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3274; Whitmore, Wittle, and Popkin, *ibid.*, 1939, **61**, 1586). The cation rearranges to the *tert.*-amyl structure so that the products, *e.g.*, ethyl *tert.*-amyl ether, formed by reaction with ethyl alcohol, and amylene, formed by internal neutralisation with the loss of a proton, are derived from the *tert.*-amyl structure, *e.g.*,

$$(CH_3)_2\overset{\beta}{C}(CH_3)\text{—}\overset{\alpha}{C}H_2\text{—}Br \longrightarrow \overset{-}{Br} + (CH_3)_2\overset{\beta}{C}(CH_3)\text{—}\overset{\alpha}{\overset{+}{C}}H_2 \longrightarrow (CH_3)_2\overset{\beta}{\overset{+}{C}}(CH_3)\text{—}\overset{\alpha}{C}H_2\text{—}CH_3$$

$$(CH_3)_2\overset{+}{C}\text{—}CH_2\text{—}CH_3 \xrightarrow{EtOH} (CH_3)_2C(OEt)\cdot CH_2\text{—}CH_3 \text{ and } (CH_3)_2C{=}CH\text{—}CH_3$$

In the rearrangement the methyl group migrates with its bond electrons, neutralizing the positive charge on the α-carbon atom (with the formation of an ethyl group attached to C_β) and creating a charge on the carbon atom (C_β) from which it leaves, thus forming the *tert.*-amyl cation. This Wagner type of rearrangement can thus be correlated with unimolecular substitution, both processes depending on a rate-determining heterolysis of the R—X bond.

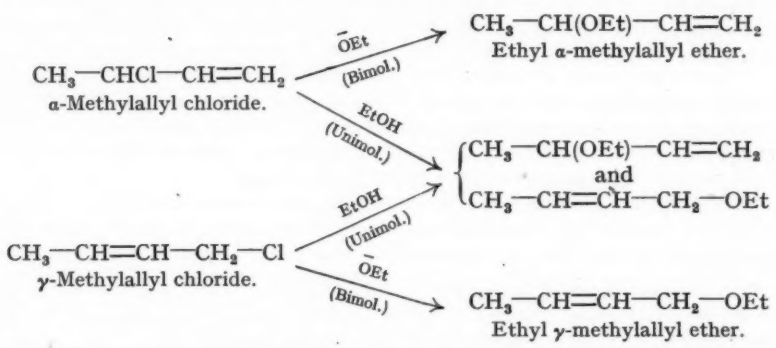
An interesting and useful form of R is one which may give rise to two products which are tautomerides in an anionotropic system. The modern theory of tautomerism supposes that interconversion usually takes place through the formation of an ionic intermediate, *e.g.*,

$$Cl\text{—}\overset{R}{\overset{|}{C}}H\text{—}CH{=}CH_2 \rightleftarrows \left[\overset{R}{\overset{|}{C}}H{=}CH{=}CH_2\right]^+ + \overset{-}{Cl} \rightleftarrows \overset{R}{\overset{|}{C}}H{=}CH\text{—}CH_2\text{—}Cl$$

Mesomeric ion.

Thus, in the system selected here for illustration, when the halogen is removed as halide ion there is a simultaneous distribution of electrons in the cation and the net positive charge is distributed. The " mesomeric " ion thus formed can then react with a chloride ion to form one or other of the two tautomers.

Now, for α-methylallyl chloride and γ-methylallyl chloride conditions can be found whereby both halides can eliminate halogen by two distinct mechanisms, recognised kinetically as the mechanisms we have designated " bimolecular " and " unimolecular." Under conditions leading to the bimolecular mechanism, the chlorides gave only the corresponding ethers. This is a direct, straightforward replacement and there is no isomerisation because the ion is never formed in the bimolecular mechanism. Under unimolecular conditions, however, both halides gave a mixture of the two possible ethers—a result entirely to be expected from an ionic mechanism :

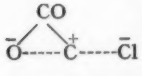


(Catchpole, Hughes, and Ingold, unpublished; cf. *Trans. Faraday Soc.*, 1941, **37**, 629.*)

Thus theories of substitution, of rearrangement, and of anionotropic change are correlated and strengthened.

(ii) *Stereochemical effects.* Evidence of mechanism may also be obtained in special cases when R is asymmetric at its point of attachment to X, the molecule R—X being optically active. We shall describe the principles here involved only in bare outline, since a fuller discussion of work relating to the steric course of substitution can be given more appropriately in the section dealing with " Applications of General Principles " (below). The method of diagnosis (of mechanism) depends essentially on the circumstance that substitution by the bimolecular mechanism (S_N2) may be expected to lead invariably to inversion of configuration, while the unimolecular mechanism may give rise, depending on structural influences, either to retention of configuration or to racemisation with a predominating inversion.

As mentioned earlier, the most favourable configuration for the transition state of a bimolecular substitution is that in which the entering and leaving groups lie on opposite sides of the α-carbon atom and on or near a straight line passing through its centre. Thus, this mechanism leads invariably to a configurational change in the product, *i.e.*, to a Walden inversion. We shall not attempt to summarise here the theoretical and experimental work which indicates the correctness of this view; it includes a now well-known demonstration involving the use of the radioactive indicator method (Hughes, Topley, and co-workers, *J.*, 1935, 1525; 1936, 1173; 1938, 209) and the conclusion is generally accepted. The consequences of the unimolecular mechanism are not quite so clear-cut, the result depending on the nature of the groups attached to the asymmetric carbon atom, but here again the experimental observation can be satisfactorily interpreted on the basis of the adopted mechanism (S_N1). When only neutral groups are attached to the reaction centre, the dominant and characteristic stereochemical result of unimolecular substitution is extensive racemisation and this is in harmony with independently derived evidence that a carbon cation will tend to take up its preferred planar configuration. Partial inversion often accompanies the loss of optical activity and this may be interpreted as an effect of the partial shielding of the cation by the receding anion, which may not be many molecular diameters away when the attack by the enveloping solvation shell or by an anionic reagent completes the substitution process before the ion has had sufficient time to assume a planar configuration. The most striking stereochemical outcome of substitution by a first-order reaction occurs in the presence of a group, such as an α-carboxylate-ion group, which can bind a cationic centre, holding it with a bond of mainly electrostatic character pending solvent attack. During the process of ionisation the charged substituent will be oriented away from the eliminated halide ion (cf. inset) and it will tend to hold the pyramidal configuration thus produced until a new group enters the position which the old one left, thus leading to retention of configuration.



With reference to the direct application of stereochemical data to the problem of establishing duality of mechanism, we shall mention but one set of experimental observations relating to the hydrolysis of the α-bromopropionate ion in alkaline solution. In this case, by suitably changing the experimental conditions, the second- and first-order reactions can be isolated and it is found that while the second-order process leads wholly to inversion, the first-order reaction gives almost quantitative retention (Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208).

* Similar results have been obtained by Young and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 2157; 1944, **66**, 421).

In the early work on the Walden inversion it was often found that different stereochemical results could be obtained by the use of different reagents, for example, silver oxide and potassium hydroxide in the replacement of halogen by hydroxyl. In fact, this was one of the favourite methods of demonstrating that a Walden inversion had occurred, *e.g.*,

$$\textit{l}\text{-Chlorosuccinic acid} \begin{cases} \xrightarrow{Ag_2O} \textit{l}\text{-Malic acid}^* \\ \xrightarrow{KOH} \textit{d}\text{-Malic acid} \end{cases}$$

(Walden, *Ber.*, 1897, **30**, 3146.)

In this example, it is obvious that either moist silver oxide or potassium hydroxide must have produced inversion, but, owing to the difficulty of relating the sign of rotation of the reactants and products to their configuration, it is impossible to say, in the absence of further data, which of the two reagents had this effect. In our experiments, carried out under kinetic control, two stereochemical results were obtained by the use of *one* reagent, namely potassium hydroxide, at different concentrations, these concentrations being such that one mechanism predominates at one extreme of concentrations and another mechanism at the other extreme, and further, since the optical data now refer to definite reaction mechanisms, we have clear indications as to which condition produced inversion and which produced retention of configuration (see also Section B, below). We have here an indication of a point which we shall develop in more detail later, namely, that the key to the apparent mysteries of the Walden inversion is to be found through a study of reaction mechanism (see especially Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Hughes, *Trans. Faraday Soc.*, 1938, **34**, 202).

(3, 2) *Variation of* X.—Convincing evidence for the concept of the duality of mechanism has also been obtained by observing the effects of changes in the group replaced (X). Since the transfer of electrons from R to X is a more uniquely fundamental feature of mechanism S_N1, the unimolecular mechanism may be expected to be facilitated relatively to the bimolecular mechanism by high electron affinity in X. Evidence bearing on this point is available. The formation of ethyl bromide from ethyl chloride and bromide ions in acetone solution is of the second order, being of the first order with respect to each of the reactants (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 475). On the other hand, the formation of ethyl bromide from triethylsulphonium bromide (also in acetone as solvent) is a reaction of the first order, the rate being independent of the bromide-ion concentration (von Halban, *Z. physikal. Chem.*, 1909, **67**, 129) :†

$$\bar{Br} + C_2H_5{-}Cl \longrightarrow Br{-}C_2H_5 + \bar{Cl} \quad \text{(2nd order)}$$

$$\bar{Br} + C_2H_5{-}\overset{+}{S}(C_2H_5)_2 \longrightarrow Br{-}C_2H_5 + S(C_2H_5)_2 \quad \text{(1st order)}$$

Evidently, the replacement of chlorine by the more powerful electron-attracting sulphonium group has produced a change of mechanism in accordance with expectations based on the particular mechanisms under discussion.

The effects of changes in the group replaced (X) may provide evidence for the duality of mechanism in another way, the method depending on the possible formation of two or more products of reaction, for example, substitution and elimination products (cf. Section B, V). In the unimolecular reactions, the products are formed from the intermediate cation $\overset{+}{R}$, while in bimolecular reactions they are formed directly from the molecule R—X. In first approximation, therefore, the result for unimolecular reactions (for example, the ratio in which the cation is partitioned between substitution and elimination) should be independent of X, while in bimolecular processes (for example, bimolecular substitution and elimination) the nature of the products may vary widely with variation of X. For the first- and second-order substitution and elimination reactions of alkyl halides and alkyl 'onium cations, the observed relationships are of the type predicted. Thus, the percentage of *iso*butylene formed in the first-order substitution and elimination reactions of *tert.*-butyl compounds varies but little when X is changed from Hal. to $\overset{+}{S}Me_2$, but the yield of ethylene obtained in the second-order reactions of ethyl bromide and the triethylsulphonium cation changes from about 1% in the former to about 86% in the latter (Ingold and Kuriyan, *J.*, 1933, 991; Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899; Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657).

(3, 3) *Variation of* Y.—The evidence of mechanism derived from observations relating to the nature of Y is similar to the evidence already discussed relating to its concentration. Since the reagent does not function in the rate-determining stage of the unimolecular process but does so in the one-stage bimolecular substitution, the rate of reaction by the unimolecular mechanism (rate of ionisation) should be independent of the nature as well as the concentration of the substituting agent, while in the bimolecular mechanism the rate must depend on the nucleophilic activity of the reagent and on its concentration. Consequently, of course, a reagent of high nucleophilic activity will favour the bimolecular mechanism. These relationships have been observed (Gleave, Hughes, and Ingold, *J.*, 1935, 236; Bateman, Hughes, and Ingold, *J.*, 1940, 1011).

(3, 4) *Solvent Variation.*—Next, we may consider the evidence derived from the observed effects accompanying solvent variation. The heterolytic substitutions with which we are concerned are characterised by important electrical transferences which occur during the course of reaction. The influence of the solvent may

* Throughout this lecture, the symbols *d* and *l* signify sign of rotation.

† Incidentally, the solvent could not possibly function as the substituting agent in this example [cf. sub-section (2) above] and the kinetic data give unambiguous evidence of mechanism.

therefore be expected to be highly important in these reactions, and, since the effect must depend on the precise manner in which the electrical transferences take place, a change of medium may be expected to affect the two mechanisms of nucleophilic substitution both absolutely and relatively to each other. The influence of the solvent may be assessed by considering the magnitude and distribution of the charges in the transition state of each mechanism in relation to those in the reactants. By making the reasonable assumptions that strongly ionising solvents facilitate an increase in the magnitude of the charges, inhibit a decrease, and retard (more weakly in this case) the distribution of a given charge, the effect of solvent variation can be correctly predicted for each of the two mechanisms in various types of reaction. The striking agreement between theory and practice may be regarded as strong evidence that the reaction mechanisms, on which the theoretical expectations are based, are firmly founded and correctly identified with respect to the observed kinetic data (Hughes and Ingold, *J.*, 1935, 252). The method is illustrated below for the reaction between an anion and an alkyl halide molecule.

Solvent Effect in the Replacement (by Anionic Reagents) of Halogen in Alkyl Halides.

	Charges in rate-determining stage of reaction.			Predicted effect of ionising media on rate.
Mechanism.	Reactants.	Transition state.	Products.	
S_N1	R–X	$R^{\delta+}\cdots\cdots X^{\delta-}$	$R^{+} + X^{-}$	Strong acceleration
S_N2	$Y^{-} + R–X$	$Y^{\delta-}\cdots\cdots R\cdots\cdots X^{\delta-}$	$Y–R + X^{-}$	Weak retardation

In mechanism S_N1, in the case of this example, a neutral reactant gives rise to an incipient formation of charges in the transition state. In mechanism S_N2, on the other hand, an existing charge in one of the reactants is dispersed in the transition state. A change to a more ionising solvent should therefore greatly facilitate the unimolecular mechanism and slightly retard the bimolecular mechanism. The facts relating to the effect of solvent variation on the rates of the first- and second-order reactions observed in the alkaline hydrolysis of appropriate alkyl halides are wholly consistent with this deduction.

The influence of the solvent in determining the mechanism should be most important in reactions of the type illustrated, in which the direction of the medium effect on rate is different for the two mechanisms. It is in such reactions that a change of kinetic form and mechanism due to a change of solvent was predicted (Hughes and Ingold, *J.*, 1935, 253) and later realised in the case of the metathetical reactions of benzhydryl halides with halide ions, which are of the second order and evidently bimolecular in acetone and of a modified first order in liquid sulphur dioxide—modified, that is, by the mass-law and ionic-strength effects characteristic of the unimolecular mechanism (Bateman, Hughes, and Ingold, *J.*, 1940, 1011, 1017).

The effect of solvent variation has also been used to establish mechanism in a somewhat different way. The method is suitable for application to those reactions ("solvolytic" reactions) in which the solvent is also the reagent. Olson and Halford (*J. Amer. Chem. Soc.*, 1937, **59**, 2644) derived a successful two-term expression for the calculation of reaction rates in binary solvent mixtures (*e.g.*, alcohol and water), namely,

$$\text{Rate} = (k_a p_a + k_w p_w) p_{RX} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where the subscripts a, w, and RX denote respectively alcohol, water, and the alkyl halide, the p's represent partial vapour pressures, and the k's are kinetic constants. Independently of mechanism, the two constants k_a and k_w, which can be derived from measurements of the rate of solvolysis at two extremes of solvent composition, will permit calculation of the rate in a mixture of any other composition. If the mechanism is bimolecular, the same two rate-derived constants should allow calculation of the composition of the substitution product, since the product is here determined in a single reaction stage the rate of which is measured. In a mixture of ethyl alcohol and water, for example, we have:

$$R{\cdot}Cl + H_2O \longrightarrow R{\cdot}OH + HCl, \quad R{\cdot}Cl + Et{\cdot}OH \longrightarrow R{\cdot}OEt + H{\cdot}Cl$$

and if the mechanism is of the bimolecular type, we may expect:

$$R{\cdot}OEt/(R{\cdot}OEt + R{\cdot}OH) = k_a p_a/(k_a p_a + k_w p_w).$$

This is found to be the case for the hydrolysis and alcoholysis of *n*-butyl bromide in water–alcohol mixtures, consistently with independently derived conclusions that these reactions are bimolecular (Bird, Hughes, and Ingold, *J.*, 1943, 255). If the mechanism is unimolecular, on the other hand, the measured rates may have no connection with the composition of the product, which is formed in a separate reaction stage. For the solvolysis of *tert.*-butyl chloride in aqueous ethyl alcohol, it has been shown (Bateman, Hughes, and Ingold, *J.*, 1938, 881) that the same pair of constants could *not* be used to calculate both rates and product compositions, consistently with earlier conclusions that the solvolytic reactions of this halide are unimolecular (see also Farinacci and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 2544; Bateman, Hughes, and Ingold, *ibid.*, 1938, **60**, 3080; Bartlett, *ibid.*, 1939, **61**, 1630).

It has been suggested (Winstein, *ibid.*, p. 1635) that Olson and Halford's rate formula should be applied on

the basis of an assumed one-stage termolecular or quadrimolecular mechanism, involving two or three solvent molecules in the transition state of reaction. It is claimed that this proposal brings rates and product compositions into harmony in the case of *tert.*-butyl chloride. However, the approximate agreement obtained between theory and experiment is of little significance here in view of the latitude which the method allows in the selection of the several additional constants now introduced, and the mechanistic model for the termolecular or quadrimolecular reactions is not impressive (see Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1008).

B. *Applications of General Principles.*

I. *Introduction and Remarks on Steric Hindrance, the Wagner Rearrangement, and Anionotropy.*—We now proceed to discuss some applications of the general principles, noting instances of experimental investigations and theoretical ideas which have developed as a result of the guidance which may be derived from the study of the kinetics and mechanism of nucleophilic substitution reactions. A full discussion of the applications which have been made in recent years is not possible but we may indicate a few of these in brief outline. It will be appreciated that we have already introduced some important examples, such as those relating to steric hindrance, the Wagner type of rearrangement, anionotropy, and the Walden inversion. In all these instances the key to the situation has been the study of mechanism. With the aid of kinetic data the occurrence or non-occurrence of the phenomena mentioned has been related to mechanism and its determining factors, structure and experimental conditions, with the result that a more rational and precise understanding of these matters has emerged. We surmise, for instance, that in future it may not be quite as fashionable as it was at one period in the past to invoke steric hindrance as an explanation for all the misunderstood eccentricities of chemical substances and their reactions. There is, of course, a proper place, and a very important place, for steric hindrance amongst the effects controlling reactivity, and a start has been made (cf. p. 972) towards a fuller and a more quantitative appreciation of its function in chemical reactions and of its scope and limitations. The new outlook on this question has already led to interesting applications in esterification, ester hydrolysis, and other reactions (see sub-section III below).

Most instances of the Wagner type of rearrangement and of anionotropic changes (p. 973) are related to the unimolecular ionisation mechanism of substitution, but this may be a suitable opportunity for emphasizing another outcome of the kinetic study of nucleophilic substitution reactions, namely, that one and the same reaction may follow different mechanisms in not very drastically altered circumstances.

II. *The Walden Inversion.*—In the example of the Walden inversion two major difficulties have been jointly responsible for the delay in the development of our understanding of the phenomenon. The first was the difficulty, already referred to, of relating the sign of rotation of the reactants and products to their configuration, which made it necessary to carry out two or more reactions in order to demonstrate the occurrence of inversion. Thus the reactions

$$l\text{-Chlorosuccinic acid} \xrightarrow{Ag_2O} l\text{-Malic acid} \xrightarrow{PCl_5} d\text{-Chlorosuccinic acid} \quad . \quad . \quad . \quad . \quad (1)$$

clearly demonstrate the occurrence of inversion (Walden, *Ber.*, 1896, **29**, 133), but it is impossible to specify without further data in which single reaction inversion has occurred, much less how it occurred. Some ingenious methods of identifying an inversion with a particular reaction have been developed in special cases, particularly by Kenyon and his co-workers, but in general this difficulty has been a serious and persistent obstacle (see *Trans. Faraday Soc.*, 1938, **34**, 202). The second difficulty was the following : The conditions which control the steric orientation of substitution must be intimately dependent on the mechanism of substitution, and until recently this had not been fruitfully studied in aliphatic compounds. We shall now attempt to describe briefly how the position has been advanced by kinetic studies.

The statement that the occurrence or non-occurrence of inversion must be closely dependent on mechanism has been amply confirmed. Bimolecular substitution invariably leads to inversion of configuration, as already explained (p. 974), and this result is so definite that it can be used as a means of relating sign of rotation to configuration in reactants and products. The stereochemical consequences of single reactions can then be deduced. For example, in bimolecular hydrolysis with aqueous potassium hydroxide, *l*-chlorosuccinic acid gives *d*-malic acid; the change of sign of rotation in this reaction therefore indicates inversion, and the retention of sign ($l \longrightarrow l$), which, under certain conditions, is observed in hydrolysis with moist silver oxide, signifies retention of configuration; and since an over-all inversion of configuration is involved in the course of the reactions with silver oxide and phosphorus pentachloride [equation (1) above] the inversion can now be assigned to the phosphorus pentachloride reaction (see *J.*, 1937, 1252). Thus, with the aid of further kinetic work on the reactions with silver salts, and so on, it becomes possible to discover the stereochemical consequences of mechanisms other than the bimolecular mechanism, particularly the unimolecular process and the analogous "silver-ion" reaction. In hydrolysis reactions in the presence of silver salts, silver ions facilitate the separation of the halogen, *e.g.*,

$$R{\cdot}Cl + \overset{+}{Ag} \xrightarrow{(slow)} \overset{+}{R} + Ag{\cdot}Cl \qquad \overset{+}{R} + H_2O \xrightarrow{(fast)} R{\cdot}OH + \overset{+}{H}$$

The process is therefore analogous to the unimolecular (S_N1) mechanism of hydrolysis and it is found to have similar stereochemical consequences. In this way, a good start has been made towards a fuller understanding

of the problem of the Walden inversion and its broader implications regarding the stereochemical course of reactions generally.

III. *Carboxylic Esterification and Hydrolysis.*—The theory of aliphatic substitution can also be applied to the problem of carboxylic esterification and hydrolysis. The application is very similar in both cases; we shall illustrate it for the case of hydrolysis which is slightly simpler to represent.

It is necessary in the first place to distinguish between " basic " reactions (*i.e.*, hydrolysis in neutral or alkaline solutions) and " acidic " reactions (*i.e.*, acid-catalysed hydrolysis). In the former the carboxylic entity which suffers reaction is R'·CO·OR, while in the latter it is $(R'\cdot CO\cdot OHR)^+$. Secondly, there are two distinct modes of bond-fission, namely, " acyl–oxygen fission " and " alkyl–oxygen fission," and, in both basic and acidic reactions, either the one or the other may take place according to circumstances. There are thus four main types of reactions as shown below :

	Basic reactions.	Acidic reactions.
Acyl–oxygen fission.....	R'·CO|—O—R	$(R'\cdot CO|—OH—R)^+$
Alkyl–oxygen fission	R'·CO—O—|R	$(R'\cdot CO—OH—|R)^+$

Finally, for certain of these reactions, two mechanisms exist which are related to each other just like the unimolecular and bimolecular mechanisms of simple nucleophilic substitution (see especially Datta, Day, and Ingold, *J.*, 1939, 838; Hughes, Ingold, and Masterman, *ibid.*, p. 840; Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686). With the recognition of these mechanisms and with full appreciation of their relationship with the substitution processes, it is possible to make rationally-based predictions as to the effect of chemical constitution and physical conditions on the reactions. Thus, to give but one example, it may be expected, and it is found, that here also the bimolecular type of mechanism only is sensitive to steric hindrance.

IV. *Aromatic Substitution.*—In a lecture on substitution some reference should be made to the important question of aromatic replacements. The field is, however, too extensive for a discussion of all the aspects involved, and a brief mention of an application of the principles which form the main theme of this lecture must suffice at this time. In the replacement of hydrogen in the aromatic nucleus, we have normally a clear example of electrophilic substitution, and the attack of the effective reagent appears in this case to be an essential condition for the expulsion of the displaced atom. This does not, however, mean that the kinetics and mechanism are always uniform. In nitration, there is, in special cases, clear evidence of a preliminary, rate-determining stage involving the nitrating agent and not the aromatic compound. We then have the striking result that the rate of nitration is independent of the concentration and of the nature of the aromatic compound, within the boundaries of this particular mechanism. There is evidence that the rate-determining change in the reagent nitric acid is the formation of the nitronium ion, $N\overset{+}{O}_2$, which is expected to be a most effective nitrating agent. The more common result is, of course, that, in addition to a dependence on the nitrating agent, the rate is dependent on the nature and the concentration of the compound undergoing substitution just as in nucleophilic replacements. The special case is reminiscent of the unimolecular ionisation mechanism of nucleophilic substitution, and the knowledge and experience gained in the study of aliphatic replacements has been of considerable assistance in our more recent investigations of the kinetics and mechanism of aromatic substitution (cf. *Nature*, 1945, **156**, 688).

V. *Elimination Reactions.*—The theory has application also to elimination reactions (see especially Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657). Substitution and elimination occur together so often as to suggest that the duality of mechanism established for substitution might have a parallel in the mechanism of elimination. This is found to be the case. Employing the nomenclature and schematic representation already explained in connection with nucleophilic substitution, the bimolecular (*E*2) and the unimolecular (*E*1) mechanism of elimination may be illustrated as follows (Y = $\bar{O}H$, $\bar{O}Ac$, NR_3, H_2O, etc.; X = Hal., SO_2R, $\overset{+}{S}R_2$, $\overset{+}{N}R_3$, etc.) :

$$Y:\!\curvearrowright\!H|\!\frown\!CR_2\!-\!CR_2\!\frown\!X \longrightarrow Y\!-\!H + CR_2\!=\!CR_2 + :X \quad (E2)$$

$$\left.\begin{array}{l} H\!-\!CR_2\!-\!CR_2\!\frown\!X \xrightarrow{\text{(slow)}} H\!-\!CR_2\!-\!\overset{+}{C}R_2 + :X \\ Y:\!\curvearrowright\!H|\!\frown\!CR_2\!-\!\overset{+}{C}R_2 \xrightarrow{\text{(rapid)}} Y\!-\!H + CR_2\!=\!CR_2 \end{array}\right\} \quad (E1)$$

With Y = $\bar{O}H$ and X = halogen or $\overset{+}{N}R_3$ we have, for instance, a representation of olefin elimination from alkyl halides and alkylammonium salts in alkaline solution. In the bimolecular reaction, a hydroxide ion or a similar nucleophilic reagent extracts a β-proton with an accompanying separation of X with its bond electrons and the formation of the olefin—the whole process constituting a synchronous mechanism. A new proof of this mechanism, involving the use of deuterium, has recently been obtained by Skell and Hauser (*J. Amer. Chem. Soc.*, 1945, **67**, 1661). During the conversion of α-phenylethyl bromide into styrene with sodium ethoxide in $C_2H_5\cdot OD$, it was shown that the unreacted bromide did not accumulate deuterium, indicating that the β-proton and the bromide ion are eliminated simultaneously, as required by the bimolecular mechanism. In unimolecular olefin formation, the rate-determining stage is the same as for unimolecular substitution.

In the elimination reaction the carbon cation loses a β-proton, this eventuality being, in suitable circumstances, concurrent with substitution by the corresponding route. Although the elimination mechanisms are similar to the substitution processes there are important differences with respect to the effects of structural and environmental factors, and a full recognition of the similarities and differences, which is only possible through a detailed study of rates and mechanism, provides valuable information concerning the important reactions of alkyl halides and similar compounds. We shall give one example relating to the reactions of the ethyl, *iso*-propyl, and *tert.*-butyl halides with potassium hydroxide in ethyl alcohol. Under these conditions the alcohol or the alkyl ethyl ether may result by substitution reactions and an olefin by the elimination process, *e.g.*,

$$CH_3{-}CR_1R_2{-}Br + R{-}OK \begin{cases} \longrightarrow CH_3{-}CR_1R_2{-}O{-}R + KBr \\ \longrightarrow CH_2{=}CR_1R_2 + R{-}OH + KBr \end{cases}$$

(R_1 and R_2 = H or Me; R = H or Et.)

It is often stated that the action of alcoholic potassium hydroxide on an alkyl halide provides a good general method for the preparation of olefins. Actually, and quite understandably when the reaction mechanisms are considered, success or failure depends very markedly on the structure of the halide and the experimental conditions. Under the most favourable conditions for elimination the ethyl halides give only 1% of ethylene (the main products being substitution products), but the *iso*propyl halides may give up to 80% of propylene, while the *tert.*-butyl halides yield 100% of *iso*butylene, provided special precautions are taken to ensure that the unimolecular mechanism, which is so facile in the last case, does not intervene. If the unimolecular reaction does intervene in the case of the tertiary halide (a circumstance which will arise in this instance if the alkali concentration is low or the alcoholic medium is not sufficiently anhydrous) then *iso*butylene formation is reduced to about 25%, this being the characteristic ratio in which the carbon cation is partitioned between elimination and substitution under these conditions. It naturally follows that for tertiary halides the unimolecular mechanism is a much more profitable proposition when substitution products are required.

VI. *Reactivity as a Function of Mechanism.*—As a final example of the application of the general principles discussed in the first main section we may take one of a general character, and one which can be readily described in outline. We have seen from several examples that even within the comparatively narrow field of nucleophilic substitution the effect of structural factors on the rate of reaction may vary in a marked degree, depending not only on the type of reaction involved but also on the mechanism of the reaction. It is obvious, therefore, that such terms as " reactive " or " unreactive " as ordinarily used in describing the behaviour of organic compounds have little significance unless the processes which are used as the criterion of reactivity are carefully described. Striking examples are encountered when we look beyond the boundaries of nucleophilic replacements to the broader fields of substitution generally. Thus, recent work by Kharasch and others has emphasized the fact that the simple, saturated aliphatic hydrocarbons, which are usually considered to be inert, participate in a number of reactions (*e.g.*, halogenation) under surprisingly mild conditions, provided these conditions are suitably chosen. In these compounds the atom which has to be replaced, namely hydrogen, is quite unsuitable for high nucleophilic reactivity at the carbon centre (reactivity towards $\bar{O}H$, for instance) and they lack the necessary activating influence (for example, a carbonyl group or an aromatic system) which is essential for facile electrophilic substitution of a hydrogen atom, but they are quite vulnerable to attack by atomic substituting agents (*e.g.*, chlorine atoms) which participate in a symmetric or homolytic fission of the C—H bond.

Conclusion.—In conclusion, it may be remarked that the sum total of evidence for the concept of the duality of mechanism in nucleophilic substitution is overwhelmingly strong. A considerable part of the discussion has been devoted to a consideration of the evidence, partly because it has been possible at the same time to indicate some of the principal characteristics and consequences of the mechanisms, but partly also because there is still not a sufficiently general knowledge of the principles of the concept of the duplexity of mechanism, and especially of the importance of ionisation as a mechanism of change—a mechanism which is operative even in cases in which the equilibrium proportion of ions is immeasurably small or inaccessible to measurement. In the section on " Applications of General Principles " we have indicated briefly but a few of the experimental investigations and theoretical concepts which have been assisted in their development by the knowledge and experience gained in the study of the mechanism of nucleophilic replacements. Other instances have been investigated, including examples of homolytic and addition reactions, for which the application of the same methods and principles has proved of value. It is a legitimate hope that the usefulness of the technique is not exhausted and that the study of the kinetics and mechanism of reactions will continue to play an important part in the development of a more comprehensive and, at the same time, a more precise understanding of chemical substances and their reactions.

The Rutherford Memorial Lecture.

DELIVERED BEFORE THE CHEMICAL SOCIETY IN THE ROYAL INSTITUTION ON MARCH 29TH, 1939.

By SIR HENRY TIZARD, K.C.B., F.R.S.

MUCH has already been written about Rutherford and much more will be written in times to come. It is not my purpose in this lecture to try to describe, much less to assess, his work as a whole, which would be beyond my powers, but rather to sketch his influence on the progress of chemistry and to leave on record a true impression of his character as well as of his genius. I shall deal at some length with those aspects of his scientific work which were of special importance to chemistry. I shall confine myself mainly to Rutherford's early life and work. The later part of his life is fresh in our memories, but we are apt to forget the way by which he reached his commanding position. Further, it was the early part of his work which relaid the foundations of chemistry.

Many members of my audience will understand and sympathise when I say that I approach the task with a sincere and profound feeling of inadequacy. I never worked under Rutherford, never shared in the smallest degree in his triumphant progress. I am merely one of many who were given his friendship, who talked and laughed with him, and who were influenced as much by his sane, unselfseeking, and happy outlook on life as by his joy and success in his work.

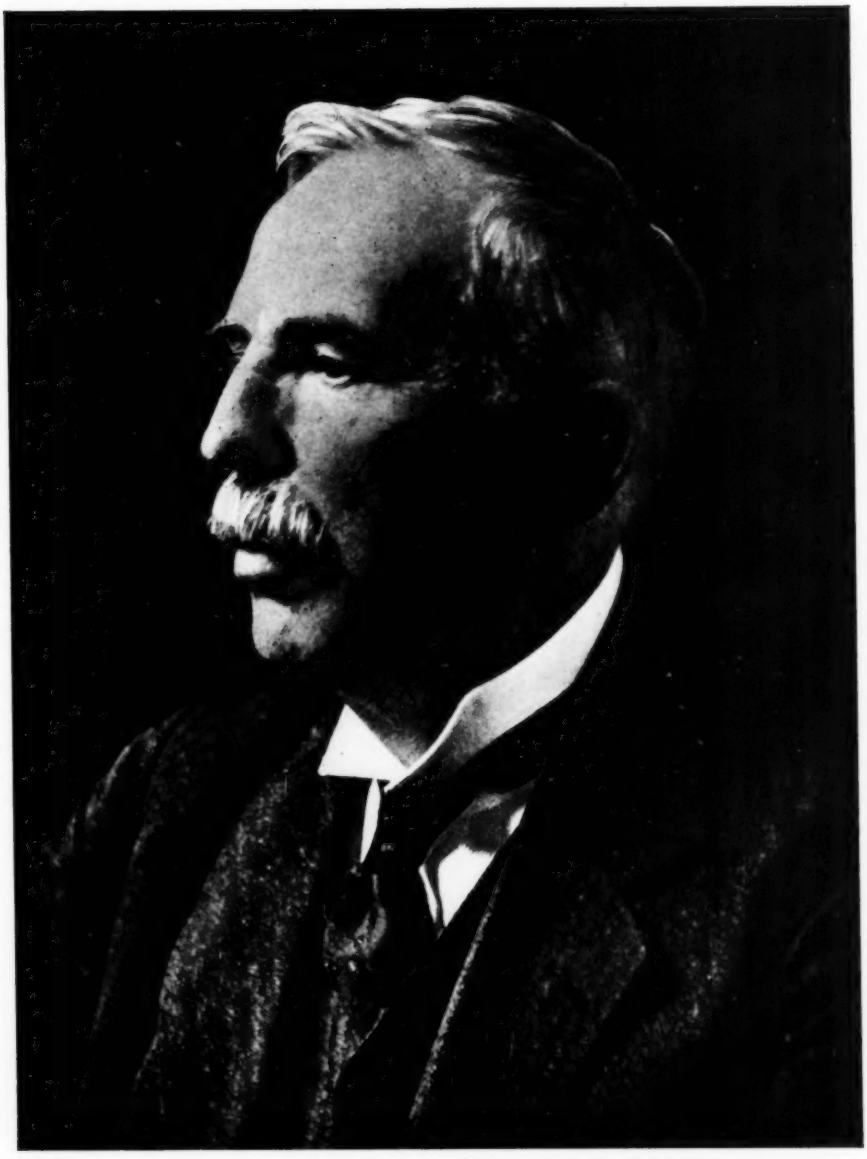
In preparing this lecture I had the curiosity to look up the first Faraday Lecture delivered in 1869 by Dumas. I found these words: " His hand, in the execution of his conceptions, kept pace with his mind in designing them; he never wanted boldness when he undertook an experiment, never lacked resources to ensure success, and was full of discreetness in interpreting results. His courage, which never flinched when once he had undertaken a task, and his caution, which felt its way carefully in adopting a received conclusion, will ever serve as models for the experimentalist."

That might equally be said of Rutherford. Which was the greater, Rutherford or Faraday, is a matter of no importance. It is enough that we put them together.

In one of his lectures Rutherford said: " In assessing the merit of any scientific discovery, it is always of much importance to view it against the background of the knowledge, and of the instrumental and technical facilities available at the time of the discovery." Let us spend a few minutes in getting a background to Rutherford's work in this way. Physics, at the beginning of the last decade of the nineteenth century, seemed to be almost finished. All the foundations had been laid; the impressive structure rested on Newton's laws, and on the fundamental laws of thermodynamics. In his Presidential address to the British Association in 1909 J. J. Thomson referred to " the pessimistic feeling, not uncommon at that time (20 years ago) that all the interesting things had been discovered, and all that was left was to alter a decimal or two in some physical constant." There were, it is true, some men who were interested in very low temperatures, and high vacua, but no one thought that these experiments would lead to a fundamental revision of first principles. Johnstone Stoney, and, more forcibly, Helmholtz, had pointed out that if the atomic hypothesis were accepted it necessarily followed from Faraday's work that electricity also was atomic in nature; but no great attention was paid to this, and there was not the slightest evidence of the nature of an atom of electricity, in spite of Crookes's speculation about a fourth state of matter. In a text book on electricity which was used for the sixth form in my School as late as 1902 there is no reference at all to the atomic nature of electricity. We spent much of our time at school studying the vagaries of the electrophorus and learning, so to speak, how to pour the positive or negative fluid of electricity from one tin can to another.

Chemistry was not so stagnant, for the natural reason that a science which was predominantly experimental in nature, and which had at its disposal some seventy elements to experiment with, could hardly ever be supposed to be coming to an end. Chemistry had also received a great stimulus from the development, by Arrhenius, of the electrolytic dissociation theory, and from van't Hoff's application of thermodynamics to chemical reactions. A new branch of the science, physical chemistry, had sprung up, and there were many active investigators, particularly in Germany, busy in uniting two sciences which had for a long time developed independently. But the history of chemistry in the nineteenth century is, in the main, the history of the development of the atomic theory, of the theory of valency, and of the periodic classification of the elements, which was begun in 1869 and later developed so brilliantly by Mendeléeff to systematise the science and to point the way to new discoveries. By 1890 the periodic system was well established, and atomic weights were known to a high degree of accuracy. But there were two alarming blots upon the system. Neither nickel nor tellurium fell into their right places. Nickel could perhaps be ignored, but tellurium was a bad blot. Its atomic weight was higher than that of iodine, not lower as it should have been. An immense amount of time and labour was spent in trying to prove otherwise, but in vain. Even as late as 1912 the question of the homogeneity of tellurium was still regarded as open. We may, I think, count it greatly to the credit of chemists that, in spite of the strongest temptation, experimental accuracy triumphed over theoretical conclusions.

The position of the atomic theory in 1894 was well summed up by Lord Salisbury in his Presidential Address to the British Association at Oxford. He said: " Of the scientific enigmas which still, at the end of the nineteenth century, defy solution, the nature and origin of what are called the elements is the most notable. It is not perhaps easy to give a precise logical reason for the feeling that the existence of our sixty-five elements is



Rutherford

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[*To face p.* 980.

a strange anomaly and conceals some much simpler state of facts. But the conviction is irresistible. . . . Many have been the attempts to solve this enigma; but up to now they have left it more impenetrable than before. . . . The theory was advanced that all these (atomic) weights were multiples of the weight of hydrogen—in other words, that each elementary atom was only a greater or a smaller number of hydrogen atoms compacted by some strange machinery into one. . . . But the reply of the laboratories has always been clear and certain—that there is not in the facts the faintest foundation for such a theory. . . . What the atom of each element is, whether it is a movement or a thing, or a vortex, or a point having inertia, whether there is any limit to its divisibility, and if so, how that limit is imposed, whether the long list of elements is final, or whether any of them have any common origin, all these questions remain surrounded by a darkness as profound as ever. The dream which lured the alchemists to their tedious labours, and which may be said to have called chemistry into being, has assuredly not been realised, but it has not yet been refuted."

The laboratory equipment available for the experimental physicist at the end of the nineteenth century was, judged by modern standards, crude in the extreme. There were no efficient accumulators available, no high-tension batteries, no convenient instruments for measuring voltage and current, no fast diffusion pumps, no valves, no Wilson cloud chamber, which Rutherford described as " that most original and wonderful instrument in scientific history." The early *X*-ray tubes were pumped out slowly and with hard labour by Toepler pumps. In his first experiments in New Zealand in 1893, on the magnetic properties of iron, Rutherford had to start every day by preparing a battery of Grove cells. Electrometers were then unreliable, capricious, and exasperating to work with. In his first book on radioactivity in 1904 Rutherford devotes the best part of a chapter to a description of the construction of electrometers and of methods of using them to ensure accuracy. All these things have to be remembered in reviewing his researches and the advance of knowledge in our time.

This then was the state of affairs when Rutherford came to England in 1895 with an 1851 Exhibition. He was then twenty-four years of age, robust, full of energy and confidence, and endowed with a fighting spirit that never left him. He arrived with one great advantage over Faraday; he had had a good education. One is tempted to add that he had an equally great advantage over many other people then and now; he had not had too good an education. He had been taught science at Canterbury College by a man who was completely unorthodox, who, it would not be unfair to say, did not know very much, but who was convinced that there was a great deal yet to be known and discovered. Bickerton must surely have credit for stimulating, if not for moulding, the genius of Rutherford, whom he left alone to pursue his own experiments on the detection of Hertzian waves in a miserable, cold, draughty, concrete-floored cellar, which was usually known to students as the " den," and in which they were accustomed to hang up their caps and gowns. One of the most famous of contemporary men of science once said to me: " If you ever think of investigating anything, don't start by looking up the literature on the subject. If you do, you will probably come to the conclusion that everything is known about it." Rutherford had little chance in New Zealand of " looking up the literature." Later in life it might almost be said that there was no necessity for him to look up the literature; he made it for himself as he went along.

He arrived in Cambridge just in time to be the first research student at the Cavendish Laboratory under a new statute allowing graduates of other Universities to become eligible for a research degree after two years' work at the University. Other young graduates there at the time or a little later were J. S. Townsend, C. T. R. Wilson, McClelland, Langevin, and H. A. Wilson. There is a group photograph of them in the Cavendish Laboratory, grim, camera conscious, and moustachioed. Contemporary memories of Rutherford are to the effect that he had the usual difficulties of a newcomer, and of a new-fangled newcomer at that, and got over them by force of character and good nature; that he worked very hard, but liked to stroll round the Laboratory and see what the other people were doing, and help them if he could; and that his own apparatus generally looked like nothing on earth, but worked. A delightful and revealing picture of his doings and ambitions at Cambridge is given in a series of letters written to his future wife, Mary Newton.

Rutherford had not been in Cambridge for long before it became quite clear, in the mature judgment of his professor and of others, that he was a man of quite exceptional originality and powers of mind. He wanted no directions; only advice and encouragement, which he got in full measure. He continued his researches on the detection of electrical waves, and developed a magnetic detector with which, within a year, he was able to receive signals at a distance of half a mile. He described and demonstrated this at the meeting of the British Association at Liverpool in 1896. Marconi, who was present, and who had been experimenting with a vertical aerial on Salisbury Plain, afterwards improved Rutherford's detector for practical use. I mention the episode, not because it has any particular importance to chemists, but because of its historical interest in indicating the probable trend of Rutherford's career if a greater fate had not been reserved for him. As it was, the discovery of *X*-rays and of the radioactivity of uranium within a few months of his arrival in England determined his life's work, and ushered in what he afterwards called the heroic age of physics.

In the early part of 1896 Rutherford started working with Thomson on the ionisation of gases by *X*-rays. In October 1896 he wrote: " I am working very hard in the Lab., and have got on to what seems to me a very promising line—very original needless to say. I have some very big ideas which I hope to try, and these if successful would be the making of me. Don't be surprised if you see a cable some morning that yours truly has discovered half a dozen new elements, for such is the direction my work is taking."

Soon after the publication of Thomson's researches on the cathode rays there appeared a paper by

Rutherford on the velocity and rate of recombination of the ions of gases exposed to *X*-rays. The great interest of this paper now is that it contains the essence of the methods by which he subsequently unravelled the mystery of radioactivity. He then went on to examine by similar methods the electrical conduction caused by uranium radiation. It had already been observed that *X*-rays are in general complex, and include rays of widely different penetrating properties. In the simplest possible way Rutherford showed that the radiation from uranium consisted of at least two types: one, which he called the alpha ray, which was very readily absorbed; and another, which he called the beta ray, of a more penetrating character.

In 1898, at the early age of 27, he was appointed Professor of Physics at McGill University, Montreal, and sailed for Canada in September, passing rich on £500 a year. By the time he left, the discovery of the electron by J. J. Thomson had provided the first definite indication that all the different kinds of matter might have a common origin.

The tale of the next few years of researches on radioactivity reads like a good detective story. Indeed it was a detective story, coming out in parts, mainly in the Philosophical Magazine, the successive numbers of which were almost snatched from the hands of the postman and read with breathless interest. False clues there were in plenty, and led many men astray; wild theories were put forward; but the great man disclosed no theory until he had ascertained the facts, and followed with unerring instinct the clue of the thorium emanation, and the clue of the alpha particle. And in the end all was made clear, and the lookers-on said: "How simple, after all. Why didn't we think of that ourselves?" At least that is what the younger lookers-on said; the older ones said: "How far fetched."

When Rutherford went to Canada the origin of the radiation emitted by uranium compounds was indeed a complete mystery, and remained so until he and Soddy put forward the famous disintegration theory in 1902. Opinions ranged from the vague view that it was a kind of phosphorescence to Crookes's fantastic suggestion that uranium had the property of "throwing off the slow moving molecules of the atmosphere while the quick moving molecules have their energy reduced." This quite natural confusion of thought, shared by men of deservedly high scientific reputations, should be remembered when we try to recall the years of frenzied, arduous, and forceful experimental work which elapsed before Rutherford arrived at the only conclusion which would satisfactorily account for all the diverse phenomena observed. It should be remembered, too, that although radium and polonium were discovered in 1898, some time elapsed before Rutherford was able to secure feeble preparations of radium only about one thousand times as active as uranium. It was not until 1903 that he managed to get 100 milligrammes of radium bromide which was about 75% pure.

I suppose that if one were to ask students of Rutherford's work which of the one hundred and fifty or so scientific papers written by him, alone or with collaborators, was the best, one would get as many varied answers as if one asked lovers of Kipling which was their favourite story. I myself, speaking perhaps with the bias of a chemist, think that no papers are more illustrative of his genius, when we take into account his age, the baffling nature of the subject, and the equipment at his disposal, than those he published on thorium radiation within a year after his arrival at McGill. In a series of simple experiments he showed that thorium gave off a kind of gas or emanation, which could be blown along a tube by a slow current of air, and detected in a testing vessel by the conductivity it produced. He showed, too, that any solid object in contact with the emanation became temporarily radioactive, and that this temporary activity decayed to half its value in about eleven hours irrespective of the nature of the surface. If metal surfaces exposed to the emanation were charged negatively, this "induced" radioactivity tended to concentrate on them. He made a fine platinum wire very active in this way, and then showed that it lost most of its activity when dipped into dilute sulphuric acid. Finally he evaporated the sulphuric acid to dryness and found that the dry glass surface was strongly active. Hence the radioactivity was not destroyed, and the only satisfactory explanation of the observations was that thorium continuously produced a minute quantity of radioactive gas, which then deposited particles of matter of a different degree of radioactivity and with different chemical properties on surfaces with which it came in contact. It was this investigation that really gave him the clue to his subsequent work which led to the disintegration theory; and this was the first time in which chemical experiments were made with a quantity of matter less than one-billionth of that which could be detected by the most delicate balance. How simple, and how beautiful. To read the papers after all these years still gives one a thrill.

Dr. Johnson once advised Boswell that a biographer should amongst other things endeavour to give an author's opinion of his own work. I can give you two opinions of Rutherford's on his work at the time. The first was written in December 1899: "I sent off on Thursday another long paper for the press which is a very good one, even though I say so, and comprises a thousand new facts which have been undreamt of . . . suffice it to say that it is a matter of considerable scientific moment." Towards the end of life he said on one occasion: "I've just been reading some of my early papers, and, you know, when I'd finished, I said to myself, Rutherford, my boy, you used to be a damned clever fellow."

Soon after the publication of this paper Soddy arrived in Montreal as a lecturer in the Department of Chemistry, and began that fruitful association with Rutherford which was to end in results so surprising and at first so unacceptable to chemists. In a series of what now seem simple investigations they showed that radioactivity must be an atomic phenomenon accompanied by the continuous production of new types of matter with distinctive chemical properties. The only reasonable explanation was that radioactive elements must be undergoing spontaneous transformation. In the light of their results they put forward the suggestion that the presence of helium in minerals containing uranium and thorium must be connected with their radio-

activity. There was no evidence at this stage to identify the alpha particle with helium. Soddy went back to England in 1903, and he and Ramsay conclusively proved, by spectroscopic evidence, that helium was a product of the disintegration of radium emanation.

Rutherford and Soddy's work was predominantly chemical in character. Indeed this is true of a large part of Rutherford's researches in Canada. The electrometer was merely the physical instrument used to detect and identify infinitesimal quantities of different kinds of radioactive matter. It was not therefore at all inappropriate that when he received the Nobel Prize in 1908 it was given for his researches in chemistry. Rutherford always professed himself highly entertained by this; but he handsomely said that he had no objection to being regarded as a chemist provided his chemical friends did not mind.

Needless to say the revolutionary theory of the spontaneous disintegration of atoms did not escape severe criticism. At Montreal it was murmured that Rutherford was bringing discredit on the University. In England Kelvin headed a band of lesser men in expressing his disapproval. Even Becquerel and Curie, who were far more entitled to express an opinion, were critical. Some years later, in 1907, Smithells expressed the opinion of many chemists when he said: " There is an uneasy feeling that developments of great importance to chemists are being made by experiments on quantities of matter of almost inconceivable minuteness." Rutherford answered the sceptics politely but forcefully. This was one of the few occasions when he troubled to answer criticisms in print. His avoidance of public controversy was one of his most remarkable characteristics; we can all imitate him in that, even if we cannot aspire to his genius.

After his first lecture at the Royal Institution in 1904 Rutherford was invited to Terling by Lord Rayleigh to meet Kelvin. Kelvin talked radium most of the week-end but would not pay attention to Rutherford's views. Rutherford had, however, a strong supporter in Strutt, the present Lord Rayleigh, who laid a modest bet of five shillings with Kelvin that he would live to change his mind. Kelvin paid the five shillings after the meeting of the British Association in 1904; rather prematurely, it appears, because two years later he wrote in a letter that " the disintegration of the radium atom is wantonly nonsensical." However, in the end he was completely converted.

After this lapse of time we can at least be as gentle with Rutherford's critics as he was, merely noting this one more striking example in the history of science, as of other subjects, how men who have had established doctrines dinned into them in youth, and have spent their lives in studying and trying to improve them in detail, violently resist a complete change in their habits of mind forced on them by a younger generation. Let us resolve to be on our guard as we ourselves grow old. What is noteworthy is the way Rutherford dealt with the situation. He suppressed his natural impatience with those who were so blind because they would not see, marshalled all his evidence, direct and circumstantial, with the skill of a great lawyer, and drove his points home one by one until he got a unanimous verdict. Later on, when he was at the height of his fame, I think we got to regard Rutherford as someone to whom Nature had imparted her secrets in a mysterious way, and that as he knew the answer to any problem beforehand it was comparatively easy to devise the experiment to prove it. This is far from the truth. He had to grope his way like anyone else, and his consistent success was due in the main to hard work and brilliant experiment; to his exceptional insight and imagination he added an infinite capacity for taking pains. He himself said on one occasion that " if you look at my work you will see that any success I have had has been due to my continually trying to press forward experimental methods little by little in every possible direction." These may not be his exact words but they express what he meant. No one who reads again his papers, or the successive editions of his books on radioactivity, or his classic Bakerian Lectures, or indeed any of his masterly reviews of progress from time to time, can fail to realise the truth of this remark.

Take for example the history of the alpha particle. In the ten years between 1899 and 1909 Rutherford published over twenty papers which dealt mainly if not entirely with the nature and properties of alpha rays. He came early to the conclusion that the alpha rays consisted of material particles projected with great velocity. He thought that they were charged particles, but would not commit himself. He made experiments to determine whether they were deviated in a magnetic field, but got at first negative results, and they were referred to for some time as the non-deviable rays. In 1902 he secured a stronger preparation of radium, and with an improved apparatus and technique showed that they were deflected by a strong magnetic field, and that they were positively charged. On the reasonable assumption that each particle carried one unit of positive electricity it followed that the mass was about twice that of the hydrogen atom, and therefore that if the alpha particle consisted of any known kind of matter it must be either hydrogen or helium. But still he was not satisfied. In 1905 he wrote to Boltwood: " I feel sure that helium is the alpha particle of radium and uranium products, but it is going to be a terrible thing to prove definitely. . . . It may conceivably be a hydrogen molecule, half atom of helium, or helium atom with two charges, and nothing but a pure scientific nose can say with certainty that one is more probable than the others. My nose (which may be prejudiced) leads me to avoid the H molecule like the devil." In 1907, after two more years' work, he was still uncertain and wrote to Hahn: " It may yet turn out that the alpha particle is hydrogen, and that helium comes from a rayless product. . . . The whole problem is very mixed."

In 1908, when he was at Manchester, he finally succeeded in counting alpha particles one by one with the Geiger counter, and in determining the number projected from radium in a given time, and the total charge, from which the charge on each particle was deduced. It was clear then that the charge was one of two units of positive electricity, and that the particle must have a mass of four. Then he got finally a direct experimental

proof by firing alpha particles through a thin glass-walled tube into a vacuum, and showing that helium was produced outside.

By the time Rutherford left Canada for Manchester in 1907 the general nature of radioactivity had been made clear, the disintegration theory was well established, and the long series of changes in uranium, thorium, and actinium was well understood. It had been shown almost certainly that lead was the final product of disintegration (an assumption which, said Rutherford in 1905, will make even the metaphysicians dizzy), and over twenty new radioactive elements of short life had been discovered. Some chemists were busy trying to fit them in to the periodic table; with considerable ingenuity places were found for some sixteen of them, but the rest had to be regarded as pseudo elements—another example of the usefulness of a knowledge of the Classics when we wish to cloak our ignorance. Within two more years it was established that uranium-X and thorium were chemically indistinguishable, that radium-D could not be separated from lead, and that there were many other cases which indicated that elements of different atomic weights could have identical chemical properties. The observations led finally to Soddy's theory of isotopes and to the displacement law, which showed definitely that the properties of the elements were not primarily determined by atomic weights, but that some broader generalisation was necessary.

The happiest part of Rutherford's life was spent at Manchester, if one can say that of a life that was always happy. He was welcomed with open arms by the University. He had many friends outside the University: the prominent business men of Manchester, then, as now, were brought up in a liberal atmosphere, had strong cultural interests, and did not judge other men solely by their salaries. The South African War was a thing well of the past, income tax had been lowered to 1/- from the unprecedented level of 1/3 in 1902, and there was every prospect of long years of peace and prosperity. Rutherford found a well equipped laboratory, a prince of research assistants in Geiger, and of laboratory stewards in Kay, and he soon gathered round him a team of able and enthusiastic younger workers. It was at Manchester that the most dramatic event of his scientific career happened—the discovery of the real nature of the atom. Rutherford was fond of telling the story. He told it again in his last lecture at Cambridge before his death, in that delightfully intimate way in which he used to talk when he felt quite at home with his audience. Marsden had been told to see if he could detect if alpha rays could be scattered through large angles when they were projected at thin sheets of metal. "I may tell you, in confidence," said Rutherford, "that I did not believe they would be." The unexpected happened, and two or three days later Geiger came along to say that some of the alpha particles had bounced backwards. "It was quite the most incredible event that has ever happened to me in my life. It was almost as incredible as if you fired a 15-inch shell at a piece of tissue paper and it came back and hit you." Rutherford went away, and by mathematical processes which I suspect a good mathematician would think crude but which were effective and sound, showed that the observation could only be accounted for if the greater part of the mass of an atom were concentrated in a volume very small compared with the apparent volume of the atom. On the assumption that this nucleus was positively charged he calculated the general laws of scattering of alpha particles, which were afterwards completely verified by experiments.

Rutherford was fully conscious that his atom should not be stable according to the current theories of electromagnetic radiation, but he was so confident of his results that that meant there was something wrong with the theory, not with the atom.* How he was justified in the event we all know. Bohr, by a theoretical investigation which Rutherford afterwards described as one of the greatest triumphs of the human mind, showed that if Planck's quantum theory, with certain assumed conditions, were applied to the Rutherford atom, the complicated relations of line spectra could be explained. His theory has been considerably modified since it was first put forward, but it quickly served to show how the Rutherford atom could account for the general properties of the different elements, and could provide an explanation of the periodic law. In more recent years it has led to a new electronic theory of valency, which has revolutionised chemistry by bringing a large number of disconnected facts into a harmonious whole and providing a new and fruitful basis for chemical research.

By 1914 Moseley's researches on the *X*-ray spectra of the elements had added evidence of the utmost importance in favour of Rutherford's and Bohr's theories, and had quickly led to the discovery of missing elements. The position, so far as chemistry was concerned, was that yet another revolution had been effected through Rutherford's work. Atomic weights were no longer the decisive factor in determining the chemical properties of elements; what mattered was the atomic number, or charge upon the central nucleus. Nickel, tellurium, and argon were no longer blots upon the periodic system, which was being replaced by a better. The uncertainty about the number of missing elements was removed; it was known there could be only ninety-two elements, distinct in chemical properties, up to and including uranium. But it was also established by then that there could be varieties of elements which differed in their atomic weights, but not in their chemical properties. Lead from radioactive minerals had been found to have a different atomic weight from ordinary lead; a severe shock for analytical chemists, hard to believe, but amply confirmed by other experiments within the next year or so. Fortunately they have long since recovered from the shock. Nature has provided that while the masses of individual atoms of elements having the same chemical properties may differ widely, the average atomic weight, with rare exceptions, is practically the same from whatever source on the earth the sample is taken.

* "The difficulty of stability is common to all theories of the atom; but what it points to is that there is something wrong with the theory of electro-magnetic radiation, not of the atom" (Rutherford, British Association, Australia, 1914).

In 1914 Rutherford's work was rudely interrupted by the War, and for the next four years he was engaged on work of immediate national importance. He got back to his own work in 1918 with renewed vigour and started at once to attack the structure of the nucleus, a problem which he had said a few years back must be left to the next generation. His efforts were quickly rewarded. Within a year he proved unmistakably that nitrogen was destroyed by alpha particles and that hydrogen was a product. From that day to this there has been a continuous and almost bewildering addition to our knowledge of the structure of the nucleus and of the transmutation of the elements. The pace was quickening even at the end of Rutherford's life. Many of the results are of no direct interest to chemistry except in so far that every advance in fundamental physics is bound to affect chemistry. What is of special interest is the discovery of heavy hydrogen and of neutrons, and the production of artificial radioactivity by neutrons and by other methods. The discovery of heavy hydrogen, or deuterium, and of the neutron, followed one of the most remarkable predictions in the history of science. " It seems very likely," said Rutherford in his Bakerian Lecture in 1920, " that one electron can also bind two H nuclei and possibly also one H nucleus. In the one case this entails the possible existence of an atom of mass nearly 2 carrying one charge, which is to be regarded as an isotope of hydrogen. In the other case, it involves the idea of the possible existence of an atom of mass 1 which has zero nuclear charge. Such an atomic structure seems by no means impossible. . . . Such an atom would have very novel properties. Its external field would be practically zero, except very close to the nucleus, and in consequence it should be able to move freely through matter. Its presence would probably be difficult to detect by the spectroscope, and it may be impossible to contain it in a sealed vessel. On the other hand it should enter readily into the structure of atoms, and may either unite with the nucleus or be disintegrated by its intense field, resulting possibly in the escape of a charged H atom, or an electron, or both." It was after some years and many abortive trials that this prediction was fulfilled. Neutrons were discovered in 1932 and heavy hydrogen in 1933. In the same year the first artificial radioactive element was discovered, " which showed," said Rutherford, " how little we know about radioactivity." The properties of neutrons were found to be just as Rutherford predicted, and the last few years have seen the production of radioactive varieties of the large majority of known elements. Every year adds to their number, and what one says today is liable to become out of date tomorrow. To the chemist, and particularly perhaps to the bio-chemist, these radioactive elements provide a means of experimental attack on problems which have hitherto been out of their reach.

So we can summarise Rutherford's influence on chemistry in the following way. By his early work on the disintegration of elements he destroyed the chemist's conception of the nature of atoms, and in doing so gave the atomic theory of matter a reality which it never had before. By his work on the scattering of alpha rays he removed the blots on the periodic system by removing its foundation and replacing it with something better. In so doing he caused the development of a new and fruitful conception of valency. By his work on the transmutation of elements he opened up an immense field of experimental work for the chemist, a field which few can doubt will yield results of the utmost importance to biology as well as to chemistry.

The secret of Rutherford's success in inspiring others lies not only in his genius but in his unselfishness. Surely there never was a great man who gave so much credit to others. This was not a quality of his later years when his reputation was established and could not possibly be affected by anyone else's reputation. It was a quality that he had from the very beginning. In his report on the thesis which Rutherford submitted when he was an applicant for the 1851 Exhibition, Professor Gray drew attention to some of Rutherford's results which were not new, but added : " As the author is most careful to acknowledge his indebtedness to others I feel sure he arrived at his conclusions independently." It was that quality that endeared Rutherford to his associates, that brought him loyalty and affection as well as admiration. He would always do anything he could to encourage others. In his last published lecture at Cambridge he said : " Scientists are not dependent on the ideas of a single man, but on the combined wisdom of thousands of men, all thinking of the same problem and each doing his little bit to add to the great structure of knowledge which is gradually being erected." There spoke the genuine Rutherford. It was for this co-operation that he worked all his life, and it was this that was not the least of his achievements.

I have heard it said that it was a pity that Rutherford had no Boswell, that no one of the many men who worked in daily contact with him made notes of his ways, of his sayings, of his few mistakes as well as his many successes, of his manners, good and bad, and of his faults as well as of his virtues. I share the feeling. His name will live for ever in the history of science, and yet one would like to feel that Rutherford himself lived in the history of our times as no man of science has ever lived before. In many ways Rutherford was indeed very like the great Dr. Johnson. He came to dominate the scientific world of his time in exactly the same way as Johnson had dominated the literary world. Like Johnson he had a deliberate and strong utterance and loved to fold his legs and have his talk out. Like Johnson he had occasional sallies of heat of temper and at times of passionate unreasonableness. He was the centre of attraction at any scientific gathering, and especially at the dinners of the Royal Society Club where some of us used to hang about in the hopes of hearing him say, " come and sit by me." Then just as people were always a little frightened of Johnson so I think we were a bit frightened of Rutherford, not because he could or would do us any harm but because we might fall short of his own standard of work and conduct. Of course, the shortcomings were there, but we preferred him not to observe them. Like Johnson, too, he never considered whether he should be a grave man or a merry man, but just let inclination for the time take its course. He had a boisterous sense of fun and a loud laugh. By precept and by example he helped to keep our minds free from cant. He hated pomposity

and artificiality. He loved simple people, and simple ways, and lived a simple life. He brushed little annoyances aside.

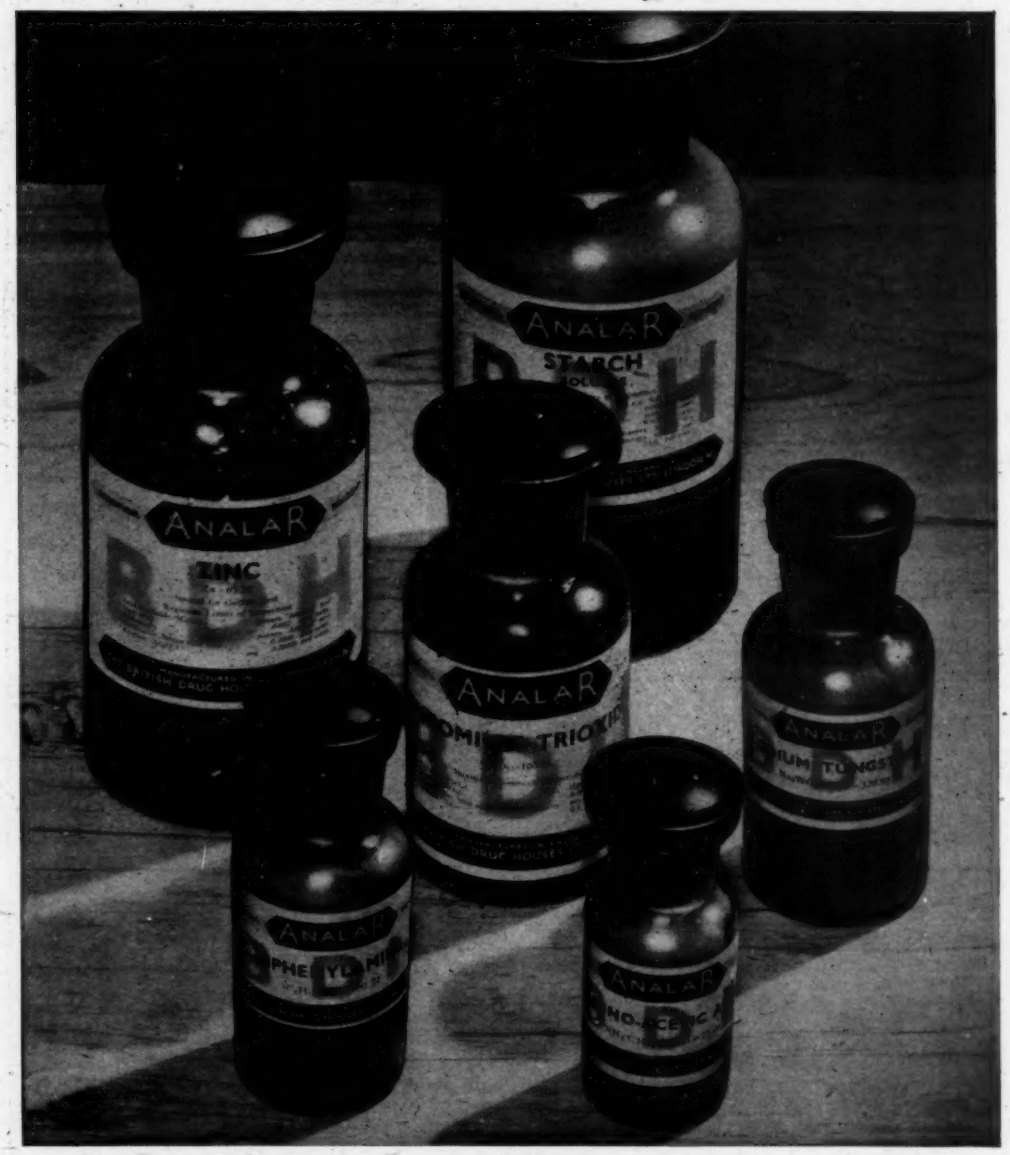
But in other respects he was very unlike Johnson. Poor Dr. Johnson suffered from ill health all his life, and was subject to severe fits of depression. Rutherford had abounding health and vigour, and there can hardly ever have been a man of such intellectual power who was so little subject to mental depression. So if we can find similarities we can also find great contrasts. Johnson lived on the whole a life of laziness interrupted by periods of feverish activity to which he was driven by lack of money. Rutherford was at the top of his form at breakfast, a thing that weaker men affect to despise, and lived a life of feverish intellectual activity relieved by short periods of magnificent idleness. When he took a holiday it really was a holiday.

There is another curious contrast with Johnson. Whereas Dr. Johnson used to relieve his literary labours by doing chemical experiments and by talking science, so Rutherford used to relieve his scientific labours by a study of literature. In his early days he was a great novel reader. When he was at Montreal, working long hours in the laboratory, the librarian found it difficult to supply him with enough light literature for his leisure moments. But later on in life he gave up the reading of novels or any form of imaginative literature, and confined himself to history and biography, to books that dealt with facts. I think he must have surprised many people from time to time by his knowledge of ancient history. He had a retentive memory, and an absurdly entertaining way of burlesquing hackneyed quotations or common proverbs, as for instance on one occasion when we were discussing short-lived reputations of men who rashly announced discoveries which were soon detected as false, he said: " Well, 'tis better to have boomed and bust than never to have boomed at all."

He took great pains in making his written papers clear and concise; they are models of what scientific papers should be. But although his writings were uniformly good and clear, Rutherford was never a good speaker except on his own subject. On formal occasions, or when he had to speak extempore, he would hesitate, fumble for words, and repeat himself. When he had to make an official speech with notes perhaps supplied by others, those who knew him well would fidget in their seats, waiting for the time when he would put the notes aside and say to himself, almost audibly, " now let's tell them about something interesting," and become himself again. But when he lectured about his own work he was superb, and unique. I expect that all who have heard him have their own private memories of him. I can almost see him now, standing in this famous lecture room, massive and commanding, demonstrating to an enthralled audience the transmutation of matter by high speed protons and deuterons. A train of valves amplified the effect of the transformation of a single atom to such an extent that it could operate a counter within sight and sound of the audience. He showed first the transmutation by protons. The counter ticked slowly as the process went on. " Now," said Rutherford, " if you will allow me, we will bombard the same target with deuterons, and I think you will observe a greatly accelerated rate of transformation." The assistants made the necessary adjustments and the current was turned on again. The counter ticked if anything rather more slowly than before, and the audience began to titter. The assistants came forward to see what was wrong. " No," roared Rutherford defiantly, " leave it alone." The words were hardly out of his mouth when the ticker obediently went off with a rush, and the audience dissolved into laughter and cheers. I was told afterwards that some of the valves used were sensitive to sound.

I hope that you will not think my stories of Rutherford unsuited to the occasion, and disrespectful to his memory. For my part I feel cheerful when I think of him, and glad to have lived in times that he made so intensely interesting; and I do not think he would wish us to be too solemn when we meet to commemorate his life and work. Besides, what I wished so much and have tried to do, was to bring back to you for a few moments the real Rutherford, as he was, his features unobscured by a smooth mask of panegyric. Of course he knew he was a great man. All his life he was like a young man rejoicing in his strength. He enjoyed, unaffectedly, the many honours that came to him, and cabled the news of each one, as it came, to his mother in New Zealand, the evening of whose long life was gladdened by the fame of her son. There was no false modesty about Rutherford; but neither was there any vanity. He never seemed to be driven by the very human motive to excel other men. His compelling passion was the search for truth.

" Well, it's a great life," Rutherford often used to say, in high spirits. It was, indeed, a great life. Happy stories will be told of him till death takes away the last of those who knew him well.



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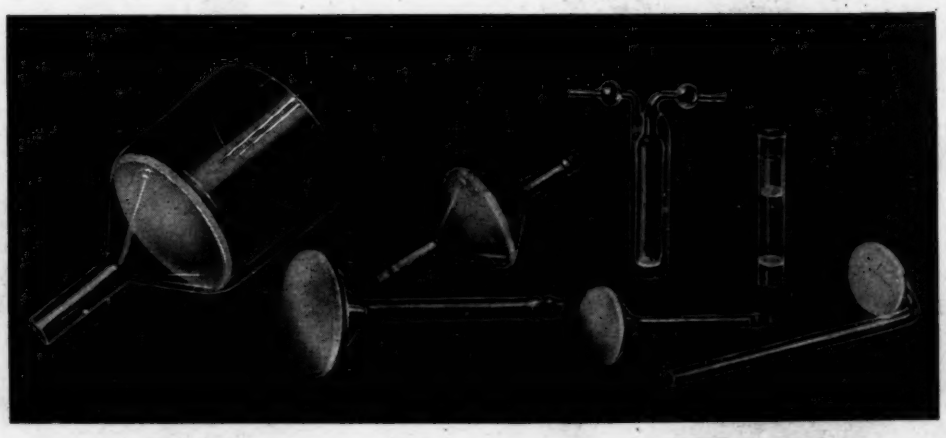

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